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THE TREATMENT OF ECZEMA IN INFANTS AND CHILDREN

PART I

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I HAVE seen a large number of infants and children with eczema, and have made it my serious business for a good many years to learn as much as I could about it. In spite of this my understanding of this disorder is not good, and the older I grow the more acutely I realize my ignorance. It occurred to me nevertheless that it might be of interest and possibly of some help to pediatricians, if I set down in a simple and practical manner what little I have learned about it, with especial reference to *treatment*. Occasionally I will discuss in detail highly theoretical matters, but only in so far as such discussion may help in the understanding of treatment. What I have to say is largely based upon my own experience, but at times I will review the work of others, and if I have had personally only moderate or little experience with any particular subject, I will say so.

It is my prime purpose to make this series of articles readable and practical, and of help to the practicing pediatrician in his everyday work. For this reason I intend to write not in formal textbook style, but more as I would talk, in so far as the editors will let me.

"Except ye utter by the tongue words easy to be understood, how shall it be known what is spoken?"
(I Corinthians 14:9.)

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DIAGNOSIS

Classification.—In order to treat eczema intelligently, it is first desirable, if possible, to find out by the history, the appearance and distribution of the lesions, the symptoms, and, possibly by skin tests and other laboratory procedures, what sort of eczema it is, for eczema is an inflammation of the skin under which are grouped a number of entities of various causation. It is true, however, that about 75 per cent of the "eczema" that is seen in infants and children is atopic dermatitis, that is, the sort of eczema which often occurs with asthma or hay fever, and to which there is a certain amount of hereditary predisposition. Other forms of eczema that may be seen in the young are seborrheic dermatitis, infectious eczematoid dermatitis, nummular eczema, contact eczema, and rarely eczematoid fungus infections.

History.—The first step in treatment is a detailed history: this is of the utmost importance. Some of the things that you want to know are as follows:

1. Do the father, mother, or any of the siblings have eczema, asthma, or hay fever? What any less closely connected relatives have or may have had is, in my opinion, of little import. If the father or mother has hay fever, the chances are that what the child has is atopic dermatitis.

2. How old was the child when the eczema began? Atopic dermatitis can begin at any age, but not commonly before the third month. "Eczema" before this age is likely to be seborrheic dermatitis, or, if in the newborn period, possibly a monilia infection. If the eczema began suddenly and the child is over 2 years old, it is often due to contact with something from the outside.

3. Upon what part of the body did it begin? Atopic dermatitis in early infancy commonly starts on the face. In children over one year old it is more likely to begin in front of the elbows and back of the knees. If it does begin in these places, it is probably due to environmental allergens rather than to foods. Monilia infections are likely to have their origin around the anus. Contact eruptions may start on any part of the body, according to what contact is causing the trouble. Seborrheic dermatitis often begins with cradle cap, and intertrigo in the axillae, groins, and around the navel.

4. What was the diet when the eczema began? What foods have been omitted from time to time? Did the removal of these foods do any good? Is the mother sure from what she has seen herself, and not from what some doctor has told her, that any food makes the eczema worse?

5. Does the child sleep on a feather pillow? Is there a dog, cat, or bird in the house? Is there a barn or hen house on the place, and if so, how near is it to the house, and how many horses or cows or sheep are there in the barn, and how many hens in the hen house? How much does the child go into either place? What is the father's occupation? Does anybody in the household ride horseback? I have seen atopic dermatitis in a young child aggravated by contact with the riding clothes of an older sister. Does contact with wool make the eczema worse? Did it begin shortly after the wearing of any new clothing? Does the child creep? Creeping, and the resulting contact with rough wool in the rugs, possibly dyes, and possibly inhalation of and contact with dust, when close to the floor, often aggravates or causes eczema. If by the appearance and distribution of the eczema (especially in babies) a contact eruption is suspected, what detergents or bleaching powders have been used in laundering the underclothes and diapers? Have plastic diaper protectors been used?

6. Is the itching very severe, or slight, or is there no itching? Atopic and contact dermatitis *always* itch; in seborrheic dermatitis there is often no itching.

7. What local applications have been used in treatment? Has any salve or lotion been used which has made the eczema worse? (See section on contact dermatitis.)

8. Has cortisone been used, and, if so, in what dosage, and for how long?

9. Does the baby keep the mother awake all night, and is she "on the

verge of a nervous breakdown''? If so, what sedatives have been given the baby and with what result? From a practical point of view these questions are very important, for in many cases treatment of the mother is as necessary as treatment of the baby, and if she is about at the end of her rope, it may be necessary to hospitalize the baby or to use cortisone for a while.

10. If the trouble suggests moniliasis, did the mother have a vaginal discharge during her pregnancy or did the baby have thrush in his mouth while in the hospital?

11. In older children who have had eczema for several years, it is of considerable importance to find out if there is any seasonal variation in its severity. This may point the way to the cause (possibly wool or dust in the winter, pollen in the summer).

12. Is the child having difficulty with schoolwork, or any other psychological trouble?

Inspection of the Skin.—The next step is a careful inspection of the skin. A trained dermatologist observes the distribution of the lesions, which may be of great importance in diagnosis, their kind, whether papular, macular, crusted, scaling, erythematous, pustular, or sharp margined, and especially the characteristics of the primary lesions, which may mean a great deal to him, and the stage of the dermatitis—acute, subacute, or chronic. Evidences of infection are particularly important to look for, and one small pustule, a subsiding paronychia, or any skin infection on the mother's face, arms, or hands may tell a good deal about the nature of the trouble in the child. All these questions go through the mind of a dermatologist automatically as he makes a diagnosis and plans treatment. The pediatrician should train himself to do likewise. If he makes a practice of setting down on the child's record some of these details, such observation will soon become as automatic for him as it is for the dermatologist.

From the history and from inspection of the skin a fairly accurate idea of the type of eczema present can usually be obtained.

Treatment in General

1. *Hospitalization.*—There are two advantages to hospitalization; these are usually outweighed by the disadvantages and I hospitalize only a small proportion of my eczema patients. The first advantage is that the patient can be seen every day, and treatment can therefore be followed more efficiently than if he is seen at longer intervals in the office. The second advantage is that the mother gets a much-needed rest. Few people have nursemaids now, and the strain on the mother is no light matter when she is continually occupied during the day with a fretful, itching eczematous baby, and often up a good part of the night with him as well. Often these poor women are exhausted. They must have a rest: hospitalization of the baby provides it.

The disadvantages of hospitalization are two:

A. *Infection:* Babies with eczema are unduly susceptible to respiratory infection; they are more likely to acquire this in a hospital than at home. This is particularly true of babies with atopic erythroderma; not

a few of these die from pyogenic respiratory and blood stream infection.

B. *Expense:* There is no use in hospitalizing a child with eczema for a few days. If any good is to come of it he needs to stay for several weeks. The expense is too much for most people, and a good part of the time is not justified by the results. If it were certain that the child could be entirely *cured* by hospitalization, almost any expense would be justified. This is not so, however, and it is common, particularly with older children where environmental allergens are likely to be involved, for them to be discharged from the hospital nearly or entirely free from eczema, and the whole thing comes back as bad as ever before they have been home a week.

As a rule, a young couple with an eczematous child can spend their money to better advantage on a good woman, or even a high school girl, to take charge of the child part of each day in order to relieve the mother than they can by letting the hospital have it. There may be, of course, circumstances which make hospitalization imperative, no matter what the expense.

2. *Nutrition.*—Although sometimes removal of certain foods from the diet helps babies with eczema, this practice should not be carried to a foolish extreme, which is too often done. The child must have an adequate, well-balanced diet, no matter whether he has eczema from it or not. If a baby with eczema is too thin (which is not usual), he should be made fatter; if he is too fat (which is common), he should be prevented from getting any fatter. The more rapidly a baby gains in weight, the more active is his eczema likely to be, and I think that a good many cases of eczema (particularly seborrheic dermatitis) are due more to eating too much food in general than to any specific food sensitivity. You are often between the devil and the deep sea in feeding a large, thriving and vigorous baby with eczema—he wants to eat more than his skin can handle. If he eats as much as he wants, his eczema is worse; if he is not fed as much as he wants, he cries all night.

3. *Itching.*—Seborrheic dermatitis and monilia infections often itch but little; atopic, contact, and nummular eczema itches a great deal. From the mother's point of view, the most important thing in treatment is to stop the itching. It is not possible to do this entirely. The local applications which have the most antipruritic effect are phenol, camphor, menthol, coal tar, and benzocaine. Of these, benzocaine is probably the best. If itching in an adult is confined to some small area, as it often is, it is possible to do a good deal for it with various local applications. The trouble is that in most babies and children with eczema, the eczema, and consequently the itching, is diffusely scattered, and so in order to control it, it would often be necessary to cover the child's whole body with an anti-itch preparation. Another trouble is that menthol, phenol, and camphor sting a good deal when first applied unless the skin is entirely unbroken, which is rarely the case in eczema. Crude coal tar is moderately antipruritic, and if the state of the eczema is such that tar is indicated for local treatment, this may relieve the

itching. The trouble with benzocaine is that it is a strong sensitizer; also it is not desirable to use it over large areas. The various antihistamine salves, which a few years ago were so often recommended for the treatment of itching, most of the time do no good. I do not usually expect to accomplish a great deal by the local treatment of itching, but probably accomplish more by the use of various tar ointments on the arms and legs and by bandaging these parts than in any other way. For small areas it has seemed to me that "Caligesic"* ointment, which contains 3 per cent benzocaine, works as well as anything; and I think that babies and children are less likely to become sensitized to benzocaine than are adults.

If there is itching with unbroken skin, as there sometimes is if the itching is due to "dry" skin, or sometimes to food sensitivity or to urticaria, the following prescription, which is clean and easy to apply, often works fairly well.

Liquor carbonis detergens (N.F.) ℥ iv
Phenol ʒ ss
Menthol gr. x
Powdered tragacanth q.s.
"Neobase"† ʒ ii
Camphor water ad ʒ viii
S. Shake well before using.

Itching at night is better controlled by a sedative given internally than by any local application, but this is often not very satisfactory either. The trouble is that many children are stimulated rather than quieted by the barbiturates, and that others, in order to be put to sleep, need a dose which is close to the danger mark. If it were a question of doing this only occasionally, there would not be much objection to it, but it has to be done every night over a considerable period. However, the barbiturate drugs are by no means without value; the ones to use are phenobarbital, Seconal, and Nembutal. Phenobarbital is slow in action—it takes about an hour before it begins to work, and the sedative effect, if it does work, is prolonged. The elixir of phenobarbital (U.S.P.) contains about ⅓ grain phenobarbital to the teaspoonful.

Seconal and Nembutal work more quickly, in about twenty minutes, but the duration of sedation is much less than with phenobarbital. The elixirs of these contain ¼ grain of the drug to the teaspoonful. There are also suppositories of each, in ½ and 1 grain strengths. A good plan is to give the baby 6 to 8 months old a dose of phenobarbital of ¾ grain about an hour before he is to be put to bed, and ½ grain of Nembutal or Seconal if he does not go to sleep or if he wakes up and fusses after he does go to sleep. Sometimes the barbiturates, when given in this way, work pretty well—more often they are not much good. Many times I have seen eczematous babies in the hospital kept by the resident in a continual state of coma by large doses of phenobarbital given "round the clock." True enough, the baby is quite comfortable, and is put out of circulation to the extent that he cannot even raise a finger, let alone scratch with it, but such treatment certainly should not be kept up for long, and should not be used in the home at all.

In about one case in twenty Benadryl will make a baby so sleepy that he will not scratch. When this works it is the best means of controlling the

*Sharp and Dohme, Philadelphia.
†Burroughs Wellcome & Co., Tuckahoe, N. Y.

itching; most of the time it is no good. The dose is 1 teaspoonful (10 grains) of the elixir two or three times during the day if needed, and twice at night, for a 6- to 12-month-old baby, with four hours between doses. The dosage that I have usually seen given is smaller than this, and is not enough.

Taking everything into consideration, it has seemed to me that chloral hydrate is the best sedative for these babies. I have used Noctec*, and start with ⅔ teaspoonful. If this does no good, the next night the dose is raised to 1 teaspoonful (7½ grains chloral), for a baby 1 year old. This is a pretty good sized dose of chloral for a baby. I have seen it do no harm. Less than this will not do much good.

4. *Restraint.*—A large amount of the skin trouble on any baby or child with eczema is caused by what he does to himself. No skin can heal when it is continually scratched and rubbed. In many hospitals the baby is "spread-eagled," that is, his wrists and ankles are wound with sheet wadding and then tied by tapes to the sides of the crib. This can rarely be done at home—the mother will not do it, and I do not much blame her. I no longer recommend it. I once saw a baby about 1 year old with severe atopic erythroderma, whose arms had been kept tied to the crib for several months. Every minute he was awake he was struggling against his bonds, and he used his arm muscles so much that his biceps became as hard and stuck out as much as those of a prize fighter. It is as well to make up one's mind that it is not possible to prevent entirely a baby from scratching and rubbing, no matter what is done. However, a good deal of it can be prevented. It has seemed to me that the use of elbow splints probably accomplishes more than anything else.* Elbow splints prevent the baby from scratching his face, and if his legs and arms are bandaged (see below), and the rest of him is kept well covered by clothes, he cannot do a great deal of scratching. It is also a good idea to put little cotton cloth bags over the hands or to put the hands in the toe of a small white cotton stocking and then to pin the other end of the stocking to the shirt, so that even if the baby does get his hands into contact with his skin, he cannot dig it with his fingernails. It is not possible to prevent rubbing of the face on the shoulder, but it can be seen to that what it is rubbed on is soft cotton and not wool.

5. *Bandaging.*—Bandaging the arms and legs is of the utmost importance, and does so much good that I would not think of treating an arm or leg eczema of any moment without it. Eczema of the popliteal or anticubital spaces, or of the wrists or ankles of older children, should always be bandaged. It is impossible to prevent outside trauma if this is not done, and good results can never be obtained in the treatment of any eczema if there is continual picking, rubbing, and scratching. To put the skin at rest and to give it a chance to heal is the first principle of local treatment. It is surprising to me to see how many people pay no attention to this. They seem to think that removal of some food from the diet or the use of a salve is enough. It never is.

The details of bandaging are important. Whatever salve is being

*Squibb's chloral hydrate preparation.

*"Wellcome sleeves," made by R. G. Goddard, 60 Argyle Rd., Albertson, N. Y.

used is applied, then a soft piece of white cotton cloth (never gauze), then a 2-inch Ace elastic bandage goes over this. When applying the bandage to a leg it is well to start it under the foot—it stays on better than if started at the ankle. In the same way, if bandaging the arm, the bandage should be started between the thumb and forefinger, then carried up around the wrist. The bandages should be considered part of the child's clothes, and are put on every day just as the clothes are, but are to be off only once in twenty-four hours to put on new salve. When bandages are taken off it is best to take off only one at a time, apply the salve, and put the bandage on again before taking off another one, so that the child cannot get at himself during the bandaging process. One minute of scratching can undo the improvement of weeks.

6. *Ultraviolet Light.*—This may occasionally help older children who have what I call "winter skins" (thick and dry), and who are nearly free from eczema in the summer, and begin to have it in the fall "as soon as the heat is turned on." These children are usually at their worst in the early spring. I have had by no means a large experience with ultraviolet light. I use it sometimes when I am at my wits' end and do not know what else to do and I think the parents need treatment, which they usually do. Ultraviolet light treatment is good medicine for the parents—it makes them feel that they are really *doing* something. Furthermore, it may actually help the child, particularly his itching. An ultraviolet light* is used, which can be bought for about $10.00. It is put into a "bridge lamp" stand and kept at a distance of 30 inches from the patient. Treatment is started with an exposure of ½ minute to the front (the child is naked), and ½ minute to the back. The time of exposure is increased a minute each day up to 20 minutes for the front, and 20 minutes for the back.

The best discussion of light treatment I know of is in that splendid little monograph of Nexmand's, *Clinical Studies of Besnier's Prurigo.* This was published in Copenhagen in 1948, but is written in English.*

Nexmand worked at the Finsen Institute and treated fifty-seven patient's with atopic dermatitis (mostly children). The light baths were given in the outpatient department every other day. If the patient tolerated the treatment, the baths were given in a series of thirty to forty, the number of treatments depending on the skin condition. Of fifty-seven patients treated, thirty-three were considerably improved.

7. *Bathing.*—It is sometimes said that babies with eczema should never be washed with water. I do not entirely agree with this. If there are many breaks in the skin the baby is likely to cry when put into water—it stings him. For such babies tub baths should not be used, but sponge baths of the diaper region, axillae, and groins can be given. If there is eczema of the arms and legs and bandages are being used, it is best to keep these parts dry. Some babies with eczema like to be put into the tub, some do not. The best thing to do is to try it and see what happens. If water irritates neither the baby nor his skin, there is no harm to it.

*General Electric.

*It could be obtained (when I got it) from Walter J. Johnson, 125 East 23rd St., New York (dealer in foreign medical books), and I recommend it highly to anyone who is seriously interested in atopic dermatitis.

8. *Soap.*—It is true that if a woman has eczema of the hands and does much dishwashing with soap, her eczema will be worse or, in some women, eczema may be actually caused in this way. I am pretty sure that I have never seen eczema in a baby or child caused by any mild soap, and I have seen no harm done to eczematous children with it unless it is used on acute, very tender areas. If it is found that soap does irritate the skin it is best to use "pHisoderm," or "pHisoHex," if any infection is present.*

Vaccination

No child with eczema should be vaccinated nor should he be exposed to a child who has been recently vaccinated. The virus of cowpox is extraordinarily contagious if the skin is broken, and most of the cases of eczema vaccinatum that I have seen have been acquired from a sibling. Direct contact is not necessary—the virus has been found in dust, and on clothes, towels, and bedclothes, and may live for *two months.*

If the mother has herpes of the lip and her baby has eczema, the baby will probably acquire Kaposi's varicelliform eruption from her, which clinically closely resembles eczema vaccinatum. If possible, mother and child should be separated until she is over the herpes: Kaposi's eruption is no light matter.

Other Immunizations.—A baby with eczema is no more likely to be upset by tetanus, diphtheria, and pertussis immunization than is any other child. However, if the eczema is severe, it is wiser to wait until it is better than to run the risk of adding insult to injury. Immunization with influenza vaccine should not be done to any child who is sensitive to egg white.

Skin Testing

It is not necessary to do skin tests on all children with eczema, and some dermatologists think that scratch or intracutaneous tests are of no value for *any* child with eczema. I do not quite agree with this, and believe that often valuable information may be obtained by scratch and intracutaneous tests, and also by patch tests, when used in the appropriate patients. However, if it seems clear from the history and from inspection that the eczema is not of allergic origin, skin testing is not indicated. Skin testing will be discussed more fully in the section dealing with atopic and contact eczema.

Dermatologists

If a pediatrician will pay some attention to eczema he can treat it quite well, and will not often need to send these patients to a dermatologist. Let him first be sure, however, that he is dealing with eczema, and not with some less common skin disease of which he probably knows nothing, such as lichen planus, psoriasis, or dermatitis herpetiformis. If there is any suspicion in his mind that such may be the case, let him send the patient to a dermatologist and save himself much embarrassment. I often do this, and am usually glad I did; some of the more uncommon skin diseases are far beyond the diagnostic and therapeutic ability of pediatricians or allergists.

(To be continued.)

*Soap substitutes made by Winthrop-Stearns, Inc., New York.

THE "PULMONARY HYALINE MEMBRANE" AS A MANIFESTATION OF HEART FAILURE IN THE NEWBORN INFANT

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THE granular eosinophilic precipitate observed in the lungs in many cases of neonatal death is technically neither "hyaline" nor a "membrane." The familiar terminology is objectionable, however, on grounds far more important than verbal pedantry. "Pulmonary hyaline membrane" and "hyaline membrane disease" center attention upon a single and possibly minor member of a highly constant group of manifestations. Indeed, this narrowing of attention may be one reason why no generally acceptable explanation has appeared to replace the "aspirated amniotic fluid" theory, which has become increasingly untenable.[1, 2, 3, 4]

The total picture in these newborn infants includes a history of rapidly increasing dyspnea and cyanosis, dilatation of the right heart and especially the right atrium, congestion of the lungs with extreme capillary engorgement, resorption atelectasis, pulmonary edema and albuminous fluid in the alveolar ducts.[5, 6] These findings would ordinarily suggest heart failure overloading mainly the pulmonary circuit —failure of the left heart. But the only recent writers who have mentioned the possibility of a primary cardiac mechanism are Winter and Gellis.[7] They dismiss heart failure because of the absence of edema, enlargement of the liver, or congestion of the systemic veins. Their argument will exclude the common type of cardiac decompensation but not acute failure of the left heart. Wilson[8] has denied that there is any proof that "the so-called hyaline membrane is a clinical entity or anything but an accidental pathological finding without specific etiological significance." Nevertheless, research at times seems concerned with explaining the single microscopic finding rather than with understanding the physiologic derangement of the sick baby. The pink-staining debris may, therefore, very plausibly prove to be "an eosinophilic herring," as Gruenwald[9] has suggested.

The present article will attempt to interpret the clinical and pathological picture associated with the hyaline membrane as something that can be predicted from the anatomic and physiologic features which are peculiar to the newborn infant. I will first summarize the usual observations in these infants and then offer a concept of the pathogenesis.

These newborn babies, who are usually premature, are described in many cases as appearing well and exhibiting no cyanosis or dyspnea during the first hour or two of life. No hyaline is found in the lung of an infant who dies during the first hour.[10] Thereafter, the amount of hyaline steadily increases, much less being found in the infant who survives only six hours than in one who survives thirty-six hours.[6] Chest x-rays taken during

this interval show a steadily increasing opacity of the lung fields. It is frequently remarked, however, that lateral x-rays show radiolucency of the anterior portion of the lungs.[9] In a patient lying on his back, of course, opacity due to congestion and cardiac edema would be expected to spare longest the anterior lung fields.

The autopsy findings are unique.[5, 6] The lungs are large, purplish red, heavy, firm, edematous, and have the consistency of solid organs. There is nothing that resembles the flabby, shrunken, pale-lilac areas of terminal resorption atelectasis which are so commonly found at autopsy later in life. Microscopically, the lungs reveal intense congestion. The alveoli have so completely collapsed that they give the appearance of solid tissue with no visible alveolar lumens. The picture is conspicuously different from what is seen in a baby who has never breathed, whose lungs always contain sufficient fluid to make the lumens of the alveoli clearly visible, the alveolar walls having what has been described as a "crumpled sac" appearance. Lungs with the "hyaline membrane" also reveal scattered respiratory bronchioles and alveolar ducts which are still patent and which contain varying amounts of granular eosinophilic precipitate. If death occurs in the first few hours of life, the so-called membrane is usually inadequate in amount and distribution to make plausible the theory that it acts as a "plug" to produce the resorption atelectasis.

The discussion of pathogenesis will be limited to premature infants, who make up 95 per cent of those who suffer from this disorder. The experimental observations of Barclay and associates,[11] of Barcroft[12] and of Reynolds[13] are generally accepted as picturing the mechanism of the circulatory changes at birth in the human infant.[14] Simultaneously with the cutting off of the placental circulation and the first breath of the newborn infant, there are important changes in the load of work imposed upon each chamber of the heart. Before birth fully half of the blood pumped into the aorta passes through the placenta.[15] When the return of this blood through the umbilical vein ceases, the volume that the right atrium must pump is reduced. This tends to cause a fall in the pressure that had previously kept open the valve flap of the foramen ovale. The pressure in the right ventricle also falls when inflation of the lungs makes the pulmonary circuit an outlet with relatively low resistance. In the left heart the changes are in the opposite direction. The rush of blood into the left atrium from the pulmonary veins increases the pressure in this chamber and ensures a physiologic closure of the valve of the foramen ovale. The pressure in the left ventricle is increased when the widely open placental circulation is cut off, and all blood must be pumped through the more resistant systemic circulation. The sudden increase in the load imposed on the left heart is dramatically demonstrated by the rapid work hypertrophy of the left heart in the first few weeks of extrauterine life.[15]

The birth of a 1,000 gram premature infant suddenly places grave demands upon three structures which have not completed their growth. The development of the pulmonary vascular bed is barely adequate for extrauterine

life. As Potter[5] has demonstrated, this is the time when the rapidly proliferating capillaries in the alveolar walls first become adequate for viability. There is hardly any margin for safety. Two muscular structures which have not finished their growth also must bear a vitally important burden at birth. The muscular wall of the left ventricle and the circular muscle of the ductus arteriosus are incompletely developed as compared with the same structures in a full-term infant. Failure of either of these muscles to fulfill the demands of extrauterine life may impose added load on the already marginal pulmonary circuit.

If there is failure of the left heart to pump out all of the blood which enters from the pulmonary circuit, or if there is failure of the ductus arteriosus to close when the aortic pressure has risen above the pressure in the pulmonary artery, the first effect will be congestion in the pulmonary vessels. No manifestations of immediate respiratory failure need appear. This stage would correspond to the first hour or two of life during which the premature infant may have good color and seem to have no respiratory distress. Yet even during this time a process begins which will have grave consequences for the incompletely developed pulmonary circulation. The limited capacity of the pulmonary capillary bed in the premature infant will cause a rise in pulmonary blood pressure as soon as there is any sizeable increase in pulmonary blood volume. This will be followed by filtration of blood serum from the capillaries into the alveolar walls and alveolar air spaces. The layer of edema fluid and blood serum imposes a growing barrier to oxygen exchange between the air and the capillaries. As the left ventricle receives blood that is less and less adequately oxygenated, progressive failure of the left heart will add further back pressure to burden the pulmonary vascular bed. The cycle of increasing pulmonary edema, increasing anoxemia, and increasing anoxia of the left ventricle will lead to complete failure of the overburdened left heart.

The anatomic and physiologic peculiarities of the newborn infant make the sequence of events and the autopsy findings conspicuously different from what is observed in a patient who dies from an attack of paroxysmal dyspnea later in life. Paroxysmal dyspnea caused by aortic regurgitation is characterized by cyanosis and violent dyspnea often leading to death from pulmonary edema, yet it never produces congestive consolidation of the lungs which is the invariable finding in hyaline membrane disease. Three exceptional features of the newborn baby make this difference understandable. (1) The muscle of the left ventricle weighs no more—and according to some observers weighs even less—than that of the right ventricle.[15] (2) Fetal channels of circulation may be reopened under appropriate conditions of pressure and anoxia. (3) The heart of the newborn infant can continue to function in an extreme state of anoxia that would be impossible even a few weeks after birth.[15]

There is no reason to suppose that the right heart, which was much less burdened, will succumb as soon as the left heart. As the left heart fails, the greater pressure in the right heart will cause a renewed right-to-left flow

through the foramen ovale, and a renewed right-to-left flow through the ductus arteriosus in case the ductus is open or in case it reopens during extreme anoxia as experimental evidence suggests.[11, 12, 15] Thus the circulation through the heart reverts to the fetal pattern. The blood flowing through the foramen ovale and ductus arteriosus by-passes the lungs, thereby reducing the pressure in the pulmonary vessels.

With the fall of pressure in the pulmonary circuit, a new process will gain the upper hand in the lung. The lung of the newborn infant has an amazing ability to absorb and remove water. In numerous animal experiments, and in a few experiments on newborn human infants, amniotic fluid has been instilled into the trachea during a single hour in an amount considerably greater than the total weight of the lungs (Potter[5, 6, 9]). This was absorbed and removed with no formation of any hyaline membrane. Resorption of edema fluid will exceed transudation from the capillaries when the pressure in the pulmonary vessels drops sufficiently. As in other cases of tissue resorption, water and electrolytes must be expected to be absorbed more rapidly than protein, with concentration of protein in the fluid that remains. Absorption of fluid from the edematous lung will continue until the alveoli are emptied of transudate, and any fluid that remains, together with its concentrated protein, is forced toward the alveolar ducts and respiratory bronchioles by the contraction of the elastic alveolar walls. The terminal resorption atelectasis with complete consolidation of the lungs represents a stage far beyond anything that can be produced by acute failure of the left heart later in life. It is dependent upon the possibility of reopening the fetal channels of circulation and even more importantly upon the amazing ability of the right ventricle to function under almost anaerobic conditions.

It is worth remembering that the eosinophilic material seen in the alveolar ducts has been precipitated by fixing solution. I do not wish to assert that the "hyaline membrane" is an artefact. Nonetheless there is as yet no proof that it is as impressively a "membrane" during life as after fixation.

One very interesting mechanism for the formation of the "hyaline membrane" has not been mentioned because there is at present no reliable information concerning the anastomosis between the bronchial artery and the pulmonary vessels at the time of birth. In the adult this anastomosis in the walls of respiratory bronchioles and alveolar ducts is exceptionally vulnerable in left-heart failure associated with pulmonary hypertension, as A. C. Lendrum and associates[16] have demonstrated. These authors point out that, in rheumatic myocarditis, hypertension and stagnation in this anastomosis may cause an exudate with the same appearance and distribution as that seen in "so-called vernix pneumonia." A similar process in the lung of the newborn infant might be the major contributor to the "hyaline membrane," though it would still require an explanation of the total process which Potter[5] has termed "congestive pulmonary failure."

At this point the principles of physics involved in the expansion of the lungs must be stated with some

care if we are to avoid apparent contradictions. The initial inflation of the lungs at birth requires a force sufficient to overcome the cohesive force of fluid holding the alveolar walls together. (I have used the term "cohesive force" to mean the sum of what is technically defined as "cohesion" plus what is technically defined as "surface tension." The actual cohesion between the alveolar walls is very slight as is clear from the small force needed to distend the lungs when water is injected into the trachea. The much larger resistance to inflation with air is caused by surface tension. It acts at the boundary between air and water in a way that suggests an elastic membrane holding shut the openings of the alveoli.) Inflation with air requires an astonishingly large negative pressure. This is usually stated to be the equivalent of 15 to 40 cm. of water pressure. Yet newborn infants—even premature infants who later develop the pattern associated with the hyaline membrane—can exert this pressure. When the "hyaline membrane disease" is fully developed, however, even the extreme efforts of the baby are of no avail in inflating the lung. Furthermore, the attempt to inflate the lungs by introducing air into the trachea or bronchi under pressure causes extreme distention of the terminal bronchioles and alveolar ducts, but causes only further compression of the alveoli.[5]

Three mechanisms for failure to get expansion of the alveoli with positive pressure have been suggested. The "hyaline membrane" might act as a plug to keep the alveoli from opening. Also the cohesive force between adjacent alveolar walls might be expected to increase when a higher protein content increases the viscosity of the fluid layer. Finally, the cohesive force between the alveolar walls is one which physicists call a "short-range force." It might be expected to increase when the fluid layer becomes almost submicroscopic in thickness as in fully developed resorption atelectasis.

These attractive theories, however, are demolished by a simple experimental study. Behrle and associates[17] studied the expansion of the lungs removed at autopsy from forty-four newborn infants. They did not introduce air by positive pressure into the bronchus but instead mounted one lung in a chamber with negative pressure, leaving the bronchus freely connected with the external air. The opposite lung was fixed for microscopic study. In only one case was a negative pressure of more than 50 cm. of water required to produce an apparently full expansion of the lung. In lungs from infants with a birth weight of less than 1,200 grams or from infants with the hyaline membrane in the control lung, the expansion was judged to be incomplete because of the failure on microscopic study to observe the thinning of the alveolar septa that was usually obtained. The alveoli were inflated with air, however, even in these cases. The photomicrographs which these authors publish are in striking contrast to the "Swiss cheese picture" of greatly dilated terminal bronchioles and alveolar ducts, isolated in solid masses of lung tissue, which is produced when air under positive pressure is forced into the bronchi.

We are now confronted with what at first may seem like a contradiction of the laws of physics. Thus, one can get identical inflation of a balloon by

applying a given positive pressure through the nozzle while the exterior of the balloon is in contact with the outside air, or by applying an equal negative pressure to the exterior of the balloon while the nozzle is connected with the outside air. Only the *difference in pressure* is of importance in inflating the balloon.

The fault in this case, however, is not with the laws of physics but with our choice of a physical model. For simplicity let us discuss not a state of equilibrium, but rather the immediate effect at the moment when positive or negative pressure is first applied to a lung. The first thing that happens as we begin to force air into the bronchus with positive pressure is that the alveolar ducts start to dilate before there is any increase in volume of the periphery of the lung. The beginning distention of the alveolar ducts compresses even more tightly the walls of the neighboring atelectatic alveoli. A similar picture of distended alveolar ducts surrounded by tightly compressed alveoli is produced also in the lung of the living baby when an attempt is made to resuscitate the infant by forcing air into the trachea under positive pressure.[5] The cohesive force between the walls of the collapsed alveoli, plus the compression transmitted from the neighboring overstretched alveolar ducts, makes the alveoli less easy to inflate than before positive pressure was applied. When we start to apply negative pressure to the exterior of the lung, however, the most peripheral parts of the lung will begin to stretch before air enters the alveolar ducts. Indeed, air will enter the alveolar ducts only to relieve the partial vacuum created by the pull which stretches the peripheral alveoli. Negative pressure on the outside of the lung, therefore, tends to reduce and not to increase the compression of the collapsed alveoli. This analysis is limited, of course, to the mechanics of the inflation of the lung with air, and the effect of positive pressure in causing collapse of the capillaries and impeding the pulmonary circulation is not our present concern.

An understanding of the inadequacy of positive pressure resuscitation still gives us no explanation for the respiratory failure of patients with hyaline membrane disease. Behrle and co-workers[17] proved that a negative pressure which even the premature infant can exert will bring air into the alveoli of a lung with advanced "hyaline membrane consolidation." Why then do the vigorous respiratory efforts fail to inflate the lung in the terminal stage of this disease? One mechanical fact explains why even violent efforts to breathe cannot bring air into these lungs. The lungs are described at autopsy as having the size of full inspiration.[5] The same impression is reported on the basis of x-ray evidence (Hardy[9]) with the remark that the diaphragm is pushed far down and flattened. Indeed, the respiratory struggles of such infants are described as suggesting severe emphysema or status asthmaticus (Clifford,[9] Hardy[9]). When the lungs are so distended by vascular congestion and interstitial edema that the diaphragm becomes essentially horizontal, no amount of effort by the diaphragm can cause any further descent. In-

deed, as the diaphragm approaches the horizontal, its mechanical efficiency in causing descent of the lung rapidly decreases, while its mechanical efficiency in causing retraction of the chest wall increases; hence we cannot be surprised that the diaphragmatic contraction in this terminal state seems to cause no movement of the lung even though the muscular contractions are strong enough to cause retraction of the lower end of the sternum.

The interpretation which has been presented has important therapeutic consequences which will either confirm the theory or else demonstrate it to be false. At present, most premature infants are placed on their backs in an incubator. They are moved or handled as little as possible. Frequently the foot of the bed is elevated to an angle of 30 degrees. From a mechanical point of view this routine has several unfortunate consequences. The position causes an engorgement of the systemic veins in the thorax which usurps part of the limited space within the chest. The position likewise forces a maximal load of venous blood upon the right heart and thereby increases the liability to congestion of the pulmonary vessels with further encroachment on the breathing space. It also adds to the hazard of pulmonary hypertension and edema. Finally, immobility predisposes to venous stasis which in itself can cause edema in the dependent portion of the lungs.

If the interpretation which has been outlined is sound, the principles of treatment for left-heart failure could logically be applied in the management of newborn premature infants before there is any evident respiratory distress. Indeed, if the positions and handling of the baby were planned with the object of avoiding overload in the thoracic veins and pulmonary circulation, it is possible that many cases of "congestive pulmonary failure" could be prevented. Treatment would require a harmonious alliance between the physician and the gravitational field. In practice it would mean that, except for very brief intervals, the position of the newborn infant during the first forty-eight hours should always be such that any excess venous blood would accumulate below the diaphragm and not above the diaphragm.

SUMMARY

The clinical and pathological findings in the newborn premature infant who dies of "pulmonary hyaline membrane disease" are interpreted as manifestations of left-heart failure. This explanation is based upon the fact that the cardiovascular system is not yet ready to make the adjustments required for extrauterine life, and that the failure to make these adjustments imposes an excessive load on a barely marginal pulmonary vascular bed. The unusual findings in this type of decompensation are explained as manifestations of the exceptional features of the newborn infant, such as the possibility of the reopening of fetal channels of circulation. If this interpretation is sound, the principles of treatment for left-heart failure could logically be included in the management of the newborn premature infant even before respiratory difficulty has appeared. Special emphasis is given to the possibility that this syndrome might be prevented if the handling and position

of the baby are so planned as to avoid overloading the thoracic veins and pulmonary circulation.*

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*If there are any who still believe that by saving the lives of very small premature infants one will merely burden the coming generation with mental defectives, the case of Sir Isaac Newton should be of interest.

Newton was extremely premature, and if his mother's statement can be trusted, his birth weight in metric equivalents must have been less than 1,000 grams. (Sir David Brewster, *Memoirs of the Life, Writings and Discoveries of Sir Isaac Newton, 1855.*)

INFANTILE CORTICAL HYPEROSTOSIS: TREATMENT WITH HORMONES

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TWO cases of infantile cortical hyperostosis are presented because of the relative newness and infrequency of this condition. One case, that of a Negro twin, had an apparent recovery within four weeks. Both patients were treated with cortisone or hydrocortisone.

Caffey first recognized this condition in 1938 and it was described by Caffey and Silverman[1] in 1945. Smyth and associates are credited by Burke and Ross[2] with independently recognizing and reporting this disease in 1946. It is characterized by: (1) onset in early infancy, (2) cortical thickening of the skeleton, most often the mandible, (3) tender swelling of the deep soft tissues overlying some of the lesions. Presenting symptoms are variable but include crying, hyperirritability, sleeplessness, fever, and pain on motion of the part, often causing a refusal to eat. Laboratory examinations usually have revealed increased sedimentation rates and leukocytosis. Pleural exudates were present in some reported patients with rib involvement.[1, 3]

The duration of the disease is from three to twelve months, having short spontaneous remissions and terminating without deformity except for occasional instances showing persistence of x-ray findings. It has been considered a benign disease, but one death apparently due to infantile cortical hyperostosis has been reported.[4]

The etiology has not been established, but the nature of the condition has led to a thorough investigation of the possibility of infection, and the results, thus far, have tended to eliminate it as a cause. Bone[3, 5] and blood[1, 6, 7] cultures have produced no organisms, biopsies were characteristic only of hyperplasia, and heterophil antibody tests[8] and studies for the usual febrile agglutinations[1, 2, 3, 8] and cold agglutinins[3] have been negative. Serological tests for syphilis have been reported negative in all instances. No evidence of tuberculosis has been noted with the exception of one report, by Burke and Ross,[2] of a patient having concomitant primary tuberculosis. Also against the infectious etiology has been lack of response to chemotherapy and the antibiotics. Scurvy as a causative factor has been eliminated by the x-ray characteristics and by normal blood ascorbic acid levels.[1, 2, 6, 8] Calcium and phosphorous blood levels, for the most part, have been normal. Some have reported increases in calcium up to 16 mg. per 100 ml., and decreases in phosphorus to 3.3 mg. per 100 ml. Alkaline phosphatase has been elevated in all reported determinations.

Other laboratory determinations reported in various investigations in-

clude serum cholesterol of 75 mg. per 100 ml., and cholesterol ester of 35 mg. per 100 ml., chlorides, as sodium chloride, of 525 mg. per 100 ml.[10] Serum proteins in one patient were 4.8 grams per 100 ml., with an A/G ratio of 2.9/1.9 grams per 100 ml.[10] Spinal fluid examinations have been normal.[2, 5, 7, 8, 9] Normal vitamin A absorption tests[10] and x-ray appearance have ruled out hypervitaminosis A as the cause. Trauma, neoplasm, and allergy have little to offer etiologically.

It has been noted in greater than usual incidence that the mother's age during pregnancy has been 30 years or more, and this has suggested a similar pattern to that noted in mongolism. Another observation, significant or coincidental, has been a frequent association of the onset with symptoms of an upper respiratory infection.

A recent theory advanced by Sidbury and Sidbury[4] suggested that it was an inherited defect of the arterioles affecting the involved areas with resulting hypoxia, causing focal necrosis of the overlying soft tissues and a proliferative reaction of the periosteum.

The actual diagnosis depends upon x-ray studies.

Treatment has been primarily limited to symptomatic relief and therapeutic trials. Antibiotics and chemotherapy have not proved helpful, but sedatives and analgesics have been beneficial. Treatment of existing anemia has been necessary in some cases. The available literature does not show any patients treated with cortisone or ACTH.

CASE REPORTS

CASE 1.—M. S., a white female, was born Oct. 24, 1953, weighing 7 pounds 1 ounce. Pregnancy and delivery were normal. She was placed on an evaporated milk formula and the neonatal progress was uneventful.

This was the third pregnancy and living child of an Rh-positive, Wassermann-negative mother, aged 26 years. The father, aged 32 years, was considered in good health, but had recovered from an undiagnosed illness existing from September, 1952, until December, 1953, this spanning the conception, pregnancy, and neonatal periods of the patient. The illness was characterized by generalized aching and particularly "bone pain" of the chest. Multiple myeloma was one consideration by his physicians, but a thorough investigation including a bone marrow examination did not bear this out. Spontaneous remission occurred with no recurrence. Siblings, aged 9 and 7 years, were in good health.

The patient had been seen regularly since birth, was on routine feedings and vitamins, and was well until March 1, 1954, when 4 months of age. At that time, two weeks after the first injection of triple toxoid immunization, she developed signs of a generalized upper respiratory infection with a mild dry cough. The temperature did not exceed 100° F. rectally, but she was unusually irritable, slept little, and ate poorly. She appeared to have pain on nursing and swallowing. Antibiotics were administered with no apparent effect. On March 19, nearly three weeks after the onset of symptoms, she developed a diffuse swelling in the area of the right temporomandibular joint and seemed even more uncomfortable. This lasted four days, when it subsided only to recur. At this time a right palpebral conjunctivitis was present with slight enlargement of several right anterior cervical and submaxillary lymph nodes.

During the following three weeks the respiratory signs improved, the edema decreased, but thickening of the mandibles, both right and left, was palpable. The discomfort persisted and

the temperature varied from 100° to 100.8° F., rectally. The rate of weight gain decreased though no actual loss occurred. X-ray films of the jaws taken during this time were interpreted as showing infantile cortical hyperostosis. No other bone involvement was detected.

On April 24, since no relief had been obtained, the patient was started on cortisone, 5 mg. four times daily. Her weight at this time was 16 pounds 13 ounces. She obtained marked relief within twenty-four hours and began to eat and rest well. The edema disappeared, though thickening of the bone remained palpable. Attempts to reduce the daily dosage produced recurrences. On May 15 repeat x-ray films revealed progression despite clinical control of symptoms. On June 5 she was changed to hydrocortisone to minimize the possibility of side effects and required the same dosage of this.

Repeated blood counts and urine examinations were normal and a tuberculin patch test was negative.

At 7 months of age she had four teeth and continued to grow and develop properly. Sept. 11, 1954, at 10½ months of age, her weight was 20 pounds 5 ounces, and length 28 inches. The triple toxoid injections were completed without incident.

X-ray films taken on September 11 were reported as "suggesting the healing stage of this disease." She still required the same dosage of hydrocortisone to keep her comfortable. This was four and one-half months after the onset of the first symptoms. There was no evidence of untoward side effects from hormone therapy.

When last seen on Nov. 26, 1954, the dosage of hydrocortisone had been reduced to 5 mg., twice daily, but could not be discontinued without recurrence of swelling and pain.

Case 2.—R. J. S., a Negro male twin, was born July 8, 1954, weighing 6 pounds 13 ounces. The twin, a male, but not identical, weighed 6 pounds 12 ounces. Pregnancy and delivery were normal and for one week their progress was uneventful.

The mother, aged 31 years, has a total of eleven pregnancies, the tenth ending in a spontaneous abortion in June, 1953, after approximately three months' gestation. Her gall bladder was removed soon after this. The first child died of pertussis at the age of 6 months. All other siblings were well. The father, aged 40 years and in good health, had an older son by a first wife.

The patient was seen at 1 week of age because of "loose stools" and at 3½ weeks for "spitting up" and constipation. Examinations were normal and formula changes helped relieve the complaints. He was seen at 6 weeks because he was fretful, restless, acted hungry, and vomited after feedings. Phenobarbital did not help, and two days later he developed swelling over the right mandible with enlargement of the anterior cervical lymph nodes. Feedings were taken poorly and he vomited and cried excessively. When hospitalized for observation, phenobarbital was given and the vomiting ceased. His weight was 7 pounds 8 ounces. X-ray films were reported as showing "cortical thickening of the right mandible, typical of infantile cortical hyperostosis with no other bones involved." The blood count was normal and at no time did he have fever.

He was started on hydrocortisone, 5 mg., four times daily, and within twenty-four hours he was asymptomatic, the edema was decreased, and he was discharged. He continued to do well and after a total of ten days the parents stopped treatment. A recurrence, though expected, did not occur and when last seen on Oct. 27, 1954, at the age of 3½ months, there had been no further symptoms. His weight was 9 pounds 7 ounces, and he was apparently in good health.

DISCUSSION

These two patients represented rather typical cases of infantile cortical hyperostosis. The onset was in

early infancy, with irritability, restlessness, and discomfort when nursing, with later development of swelling over the mandible. Fever was minimal or absent and blood counts and urinalyses were within normal limits. The ages of the mothers were 26 and 31 years, respectively, and that of the fathers, 32 and 40 years. Diagnosis was confirmed by x-ray studies in each case. Dentition, growth, and development were normal in patient 1 and growth and development were normal in patient 2.

Since control of symptoms by prolonged analgesia or sedation did not seem practical or safe, hormone therapy to relieve the disability and discomfort appeared to be justified.

The response to cortisone and hydrocortisone was almost immediate in each instance, with no side effects noted.

It could not be said that the course was shortened in patient 1, though symptoms were controlled. The disease in patient 2 was of very short duration. This suggested two possibilities, the most probable one being that without treatment it might have been a short illness that could have passed unrecognized, as no doubt many cases have. The other possibility was that the treatment actually shortened the course of the disease. Recurrences have, however, been reported following remissions of this duration.

SUMMARY

Two patients with infantile cortical hyperostosis, treated with hormones, are presented. One patient, a Negro infant, went into remission with a short course of hydrocortisone, with no recurrence up to the time of this writing. The other patient's course was not shortened, but symptoms were well controlled by the use of cortisone and hydrocortisone.

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CLINICAL STUDIES WITH GLUCAGON IN CHILDREN

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THE observation by Murlin and associates[1] in 1923 of transitory hyperglycemia immediately following intravenous administration of certain pancreatic extracts led to discovery of the hyperglycemic-glycogenolytic factor of the pancreas termed glucagon. Bürger and associates[2] demonstrated that glucagon is a protein polypeptide, chemically closely allied to crystalline insulin, and that hyperglycemia results from a direct glycogenolytic action in the liver. In 1953, Staub and associates[3] succeeded in purifying and crystallizing glucagon. It is the purpose of this paper to present our observations on the effects of glucagon in thirty-four children, consisting of a control group and patients with liver disease, glycogen storage disease, and spontaneous hypoglycemia.

PROCEDURE

The clinical material consisted of sixteen normal subjects, eight with liver disease, six with glycogen storage disease, and four with spontaneous hypoglycemia. They ranged from 2 months to 13 years in age. There were sixteen males and eighteen females.

Glucagon† was supplied in 10 c.c. vials which were constantly refrigerated. The solution contained 0.95 mg. of glucagon per cubic centimeter (Lot No. 208-158B-214) and the standard dose used for all tests was 20 μg per kilogram of body weight. All subjects were fasted overnight, and two to three days elapsed between tests. Blood sugar determinations were done by the micrometric method on capillary blood, using a modified Folin-Wu technique.*

NORMAL SUBJECTS

Table I shows that glucagon produced consistent blood sugar elevation ranging from 22 to 68 mg. per cent, with an average of 54 mg. per cent, thirty minutes after subcutaneous drug administration. The average one-hour blood sugar level was 25 mg. per cent with only Case 9 showing a value below the fasting value. Three subjects studied in greater detail showed that the peak effect of subcutaneously administered glucagon occurred between twenty and thirty minutes after injection, with substantial elevation within ten minutes.

The standard dose (20 μg per kilogram) was doubled and the hyperglycemic results of the 20 and the 40 μg per kilogram dosage compared in Fig. 1, which shows that this increase in dosage did not increase the hyperglycemic response. Our data are in agreement with the work of Louve and co-workers[4] who were also unable to show increased hyperglycemic effect with increased dosage. Both adrenocorticotrophic hormone and Adrenalin

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†Generously provided by Eli Lilly and Company, Indianapolis, Ind.

*Folin, J.: J. Biol. Chem. 86: 173, 1930.

increased the potency of the hyperglycemic effect of glucagon. In Fig. 2, the blood sugar response in the same subject is compared, following glucagon, Adrenalin, and combined Adrenalin-glucagon administration. twice the peak value obtained with each drug individually, and lasted longer than with either drug alone. Glucagon did not inhibit cardiovascular effects of Adrenalin, such as tachycardia or vasoconstriction.

TABLE I. CONTROL TOLERANCE TESTS IN SIXTEEN SUBJECTS, USING 20 μG PER KILOGRAM OF GLUCAGON, SUBCUTANEOUSLY, WHICH SHOW AN AVERAGE BLOOD SUGAR ELEVATION OF 54 AND 25 MG. PER CENT AT THE THIRTY- AND SIXTY-MINUTE INTERVALS, RESPECTIVELY

		BLOOD SUGAR CONCENTRATION, MG. PER CENT			
			TIME AFTER DOSE		
CASE NO.	AGE YR.	FASTING	30 MIN.	60 MIN.	120 MIN.
1	1	53	119	105	81
2	1	47	69	53	53
3	2	42	95	88	61
4	2	81	143	110	95
5	3	115	100	172	118
6	4	100	149	122	97
7	5	68	128	93	73
8	5	87	155	102	78
9	5	89	153	66	61
10	6	131	173	137	95
11	8	92	159	149	–
12	8	95	149	111	97
13	8	88	156	136	66
14	12	105	146	108	108
15	12	106	158	127	95
16	13	59	105	89	61

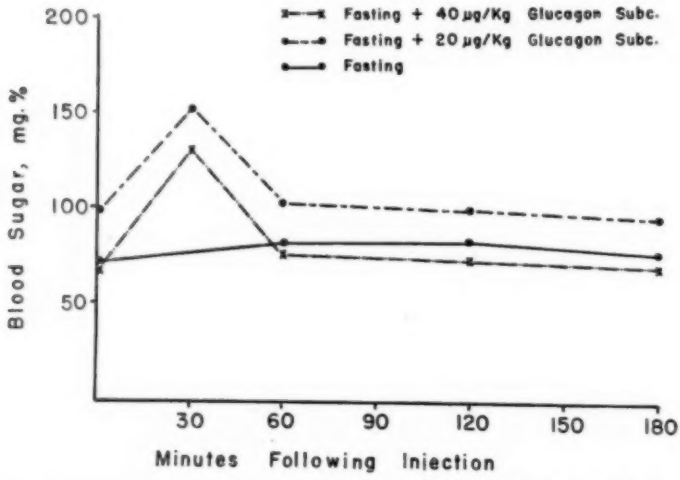

Fig. 1.—Glucagon tolerance curves with subcutaneous 20 and 40 μg per kilogram doses, showing no additive hyperglycemic effect with increased dosage.

Following simultaneous Adrenalin and glucagon administration, the maximum hyperglycemia was approximately

The anti-insulin effect of glucagon was studied in seven subjects. Fig. 3 illustrates typical curves obtained in

four subjects who had been given 0.25 unit of subcutaneous insulin per kilogram of body weight prior to glucagon administration. Within thirty minutes after insulin injection, the blood sugar dropped 26, 21, and 20 mg. per

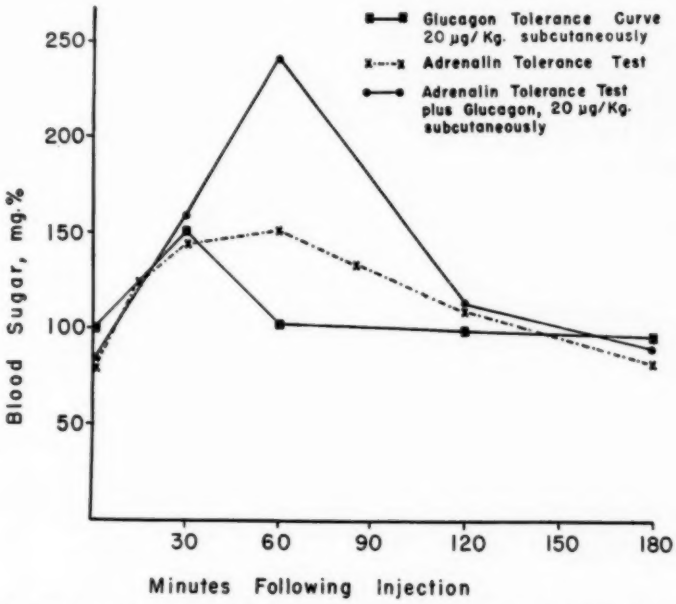

Fig. 2.—The hyperglycemic effect of glucagon, 20 µg per kilogram subcutaneously, is additive to the hyperglycemic effect of simultaneously administered subcutaneous Adrenalin.

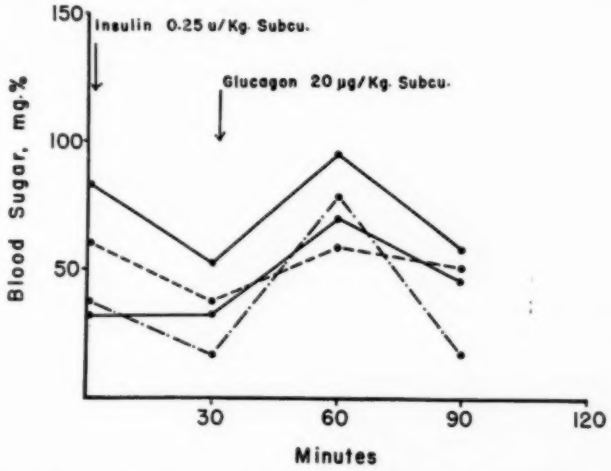

Fig. 3.—Insulin-glucagon tolerance curves demonstrating the anti-insulin effect of glucagon when administered thirty minutes after insulin.

cent, respectively, in three patients, remaining unchanged in the fourth. Glucagon (20 μg per kilogram) was then given subcutaneously, and within thirty minutes a 35 to 40 mg. per cent increase in blood sugar concentration was noted in all four subjects.

Insulin tolerance tests were performed on three subjects for comparison with combined insulin-glucagon tolerance tests. In the latter, both drugs were administered simultaneously. The results, listed in Table II, illustrate that glucagon was able to counteract the hypoglycemic action of insulin. In the control insulin tolerance tests, a drop of 19, 17, and 2 mg. per cent, respectively, was noted thirty minutes after insulin administration. When glucagon was given simultaneously with insulin, the tests resulted in a 19, 32, and 37 mg. per cent rise at thirty minutes. The one- and two-hour blood sugar levels in the glucagon-insulin tolerance tests were slightly lower than those in the insulin tolerance tests.

TABLE II. COMPARISON OF GLUCAGON, INSULIN, AND INSULIN-GLUCAGON TOLERANCE TESTS, USING 20 μG PER KILOGRAM OF GLUCAGON AND 0.25 UNIT PER KILOGRAM OF INSULIN, SUBCUTANEOUSLY, SHOWING THAT GLUCAGON COUNTERACTS INSULIN-INDUCED HYPOGLYCEMIA

CASE NO.	TOLERANCE TEST	BLOOD SUGAR			
		FASTING	RISE OR FALL AFTER TEST DOSE, MG. PER CENT		
			30 MIN.	60 MIN.	120 MIN.
13	Glucagon	88	68	48	−22
7	Glucagon	68	60	25	5
16	Glucagon	59	46	30	2
13	Insulin	86	−19	−19	−7
7	Insulin	100	−17	−12	−22
16	Insulin	88	−2	−17	−21
13	Insulin-glucagon	91	+19	−29	−38
7	Insulin-glucagon	89	+32	−23	−28
16	Insulin-glucagon	93	+37	−14	−23

PATIENTS WITH LIVER DISEASE

Since glucagon produces hyperglycemia by glycogenolysis of liver glycogen,[5] it was of interest to observe the effect of glucagon in eight patients with liver disease. In all but one patient, the diagnosis was established by surgical biopsy. Cases 1, 2, and 3 had biliary atresia with cirrhosis; Case 4 had cirrhosis of unknown etiology; Case 5 had a hamartoma replacing most of the liver, associated with hepatic insufficiency; Case 6 had inspissated bile syndrome without cirrhosis; Case 7 had acute hepatitis; and Case 8 had an undiagnosed hepatomegaly. In Case 8 liver biopsy revealed increased glycogen stores, but a definite diagnosis of glycogen storage disease could not be established. The Adrenalin tolerance test in this latter case was normal and there was no associated hypoglycemia or acetonuria. Table III shows that the four subjects with hepatic cirrhosis and the subject with hepatic insufficiency due to replacement of liver tissue by hamartoma cells had from 13 to 24 mg. per cent hyperglycemic response to glucagon administration. The remaining three with inspissated bile syndrome, acute hepatitis, and undiagnosed hepatomegaly had 41, 47, and 28 mg. per cent blood sugar elevation, respectively. The patients with inspissated bile syndrome and acute hepatitis responded norm-

ally in spite of rather severe icterus, with serum bilirubin levels of 14 and 8 mg. per cent, respectively.

well known that the Adrenalin tolerance test in this disease usually shows a flat curve. Since Adrenalin and

TABLE III. GLUCAGON TOLERANCE TESTS IN EIGHT PATIENTS WITH LIVER DISEASE, USING THE STANDARD DOSE OF 20 μG PER KILOGRAM, SUBCUTANEOUSLY, SHOWING THE IMPAIRED HYPERGLYCEMIC RESPONSE IN FIVE PATIENTS AND A NORMAL RESPONSE IN THREE OTHERS

CASE NO.	AGE (YR.)	WEIGHT (KG.)	DIAGNOSIS	BLOOD SUGAR, MG. PER 100 ML., MIN. AFTER DOSE				
				FASTING	30 MIN.	60 MIN.	120 MIN.	180 MIN.
1	3/12	5	Biliary atresia with cirrhosis	105	118	92	98	110
2	1	7	Biliary atresia with cirrhosis	67	86	74	69	67
3	9/12	6	Biliary atresia with cirrhosis	72	96	72	69	62
4	8	30	Hepatic cirrhosis	55	57	70	53	80
5	12	30	Hamartoma	55	65	70	60	65
6	2/12	3	Inspissated bile syndrome	87	128	92	82	--
7	7	25	Acute hepatitis	90	137	95	90	--
8	1	8	Hepatomegaly undiagnosed	93	121	109	102	84

TABLE IV. COMPARISON OF ADRENALIN AND GLUCAGON TOLERANCE TESTS IN SIX PATIENTS WITH GLYCOGEN STORAGE DISEASE, SHOWING VARIABLE HYPERGLYCEMIC RESPONSE TO ADRENALIN OR GLUCAGON ADMINISTRATION

CASE NO.	PATIENT	AGE (YR.)	BLOOD SUGAR TIME IN MINUTES AFTER DRUG INJECTION				
			FASTING	30 MIN.	60 MIN.	120 MIN.	180 MIN.
	Adrenalin Tolerance Test: ½ minim/kg., subcutaneously						
1	C. S.	2	53	55	55	74	55
2	T. S.	9	40	39	40	44	46
3	J. S.	8	73	74	92	93	--
4	K. H.	7	53	62	70	90	53
5	D. B. (Danniel)	7	94	154	157	132	126
6	D. B. (Dennis)	7	87	126	180	111	114
	Glucagon Tolerance Test: 20 μg/kg., subcutaneously						
1	C. S.	2	55	90	80	60	55
2	T. S.	9	32	26	26	42	51
3	J. S.	8	63	74	70	70	58
3	J. S. (I. V.)	8	69	79	77	69	87
4	K. H.	7	59	89	86	64	--
5	D. B. (Danniel)	7	89	96	148	103	--
6	D. B. (Dennis)	7	81	89	89	89	--

Cases 1 and 2 were referred to us for study by Henry G. Kurz, M.D., La Habra, Calif.
Case 3 was referred to us for study by Paul Starr, M.D., Pasadena, Calif.
Case 4 was referred to us for study by James N. Yamazaki, M.D., Los Angeles, Calif.
Cases 5 and 6 were referred to us for study by Vincent Rounds, M.D., Redondo Beach, Calif.

PATIENTS WITH GLYCOGEN STORAGE DISEASE

Cori and Cori[6] have shown that several types of glycogen storage disease exist. They have shown a specific deficiency of glucose-6-phosphatase in two cases[6] and structural abnormalities of the glycogen[7] in two others. It is

glucagon both cause glycogenolysis of liver glycogen by increased phosphorylase activity,[8] it is reasonable to assume that the hyperglycemic effect of glucagon would be absent in the patients with this disease. Six patients were accordingly tested with the standard dose of 20 μg per kilogram of

glucagon and the results of this test were compared with those obtained with standard Adrenalin tolerance tests. Table IV shows the low Adrenalin tolerance tests in Cases 1, 2, 3, and 4. Case 1, the sibling of Case 2, has clinical signs and symptoms of glycogen storage disease, although liver biopsy has not been performed. Case 2 has been studied by Illingworth and Cori[7] and shown to have normal liver glycogen. Unfortunately, not enough liver tissue was secured for determination of glycogen content of liver tissue, or for specific enzyme studies. Cases 3 and 4 have clinical signs and symptoms of the disease, as manifested by hepatomegaly, poor growth, acetonuria, flat Adrenalin tolerance tests, and surgical biopsies, showing increased glycogen stores by histologic methods, but not by chemical determination. Cases 5 and 6 are fraternal twins studied by Illingworth and Cori[7] and shown to have normal liver glycogen. Glycogen determinations in these two cases were 14.2 and 12.7 per cent, respectively, compared to control values of 0.56 to 4.6 per cent.[7] Cori and Cori[8] studied a biopsy specimen obtained from Case 6 and showed a marked reduction in glucose-6-phosphatase activity. Table V shows that Cases 1, 4, and 5 had a 35, 30, and 59 mg. per cent response to glucagon administration, whereas Cases 2, 3, and 6 failed to reveal any hyperglycemic response to glucagon. Case 3 was also given intravenous glucagon without hyperglycemic response.

PATIENTS WITH SPONTANEOUS HYPOGLYCEMIA

It is currently believed that patients with idiopathic hypoglycemia are unable to mobilize enough blood sugar to relieve their symptoms during a hypoglycemic convulsive episode. Glucagon, however, is able to mobilize glycogen stores and raise the blood sugar even in the presence of exogenous insulin. From this, it was postulated that glucagon might be able to counteract the acute hypoglycemic episodes which characterize this disease.

Four patients with idiopathic hypoglycemia were studied. The diagnosis in each was based upon the clinical and laboratory observations of repeated episodes of spontaneous hypoglycemia and abnormal sensitivity to exogenous insulin, as demonstrated by insulin tests. Table V shows that glucagon tolerance tests in these patients

TABLE V. GLUCAGON TOLERANCE TESTS IN SIX PATIENTS WITH SPONTANEOUS HYPOGLYCEMIA USING 20 μG. PER KILOGRAM OF GLUCAGON, SUBCUTANEOUSLY, AND COMPARING THE HYPERGLYCEMIC RESPONSE BEFORE AND AFTER THE INSTITUTION OF ADRENOCORTICOTROPHIC HORMONE AND HYDROCORTISONE THERAPY

CASE NO.	AGE (YR.)	BLOOD SUGAR VALUES, MG. PER 100 ML., MINUTES AFTER DRUG INJECTION				
		FASTING	30 MIN.	60 MIN.	120 MIN.	180 MIN.
1	1½	65	127	97	43	47
2	4	58	100	72	68	--
3	4	69	132	69	69	64
4	2	69	95	53	53	--
		One week after ACTH therapy				
1	1½	65	132	115	91	90
2	4	60	165	81	62	84
3	4	90	138	110	100	--
		One week after hydrocortisone therapy				
4	2	92	114	95	60	--

produced an initial, normal hyperglycemic response at the thirty-minute interval. At the two-hour interval, the blood sugar concentration had returned to or below the original fasting level. After the patients were placed on adrenocorticotrophic hormone, 1 mg. per kilogram per day of the gel form, the initial hyperglycemic response was prolonged. In subsequent insulin tolerance tests, neither a single dose of glucagon nor steroid therapy completely protected these patients from the hypoglycemic effect of insulin. However, multiple doses of glucagon have been successfully used to terminate hypoglycemic convulsions in these patients.

DISCUSSION

Glucagon is a polypeptide differing from insulin primarily in its amino acid content.[9] Methionine and tryptophane are present in glucagon but not in insulin. Cystine, isoleucine, and proline are present in insulin but not in glucagon. The drug is readily utilized subcutaneously and is also effective when given intravenously. It is relatively nontoxic in the dosage used in our studies.

Glucagon has been found in pancreatic extracts of a variety of animals.[10] Its distribution in the pancreas is similar to that of islet tissue in that it is more abundant in the tail of the pancreas and in the fetal pancreas. Pancreatic duct ligation or alloxan administration does not change the gland's glucagon content.[11] Fodden and Read,[12] in 1954, showed that Synthalin A (decamethylenediguanidine) produces vacuolization in the alpha cells of the pancreas and that extracts from pancreas treated in this manner do not contain glucagon. These observations lend support to the theory that the alpha cells of the pancreas are the site of glucagon production.

Specific glucagon action is thought to be mediated by increased phosphorylase activity, which makes more glucose-1-phosphate available for glucose production[15] (see Fig. 4). As little as 10 μg produces a significant elevation of blood sugar concentration.[11] Further proof that the site of action of glucagon is in the liver is furnished by hepatic vein catheterization studies which showed that glucagon administration results in a prompt increase of hepatic vein glucose, as compared with peripheral blood glucose values.[13] In addition, glucagon has no hyperglycemic effect in the hepatectomized animals[14] or the eviscerated rat.[15] In contrast to Adrenalin, glucagon has little if any effect on muscle glycogen.[16] Glucagon and Adrenalin also differ in the glycogenolytic response to dihydroergotamine which is an adrenergic blocking drug.[17] It has been shown in rabbit liver slices that this drug is capable of blocking the glycogenolytic effect of Adrenalin but not of glucagon.

After Staub and co-workers[3] succeeded in purifying and crystallizing glucagon in 1953, experimental work in the human being became possible. The drug has been nontoxic in our hands, except when given intravenously continuously over a period of four hours at a 20 μg per kilogram per hour dosage. Nausea and vomiting without hypoglycemia occurred in three patients so treated. Itching was noted at the site of injection in two cases.

Glucagon consistently produced hyperglycemia in our series of normal control subjects. The intravenous and subcutaneous routes produced predict-

able results. The intramuscular route was not investigated; however, Kirtley[9] has used this route of administration and found it satisfactory in adults.

Utilizing in vitro studies with liver slices, Sutherland[8] tested Adrenalin and glucagon together, in supramaximal amounts, and was unable to demonstrate more hyperglycemia than with either substance alone. Our in vivo studies clearly showed an additive effect. Blood sugar levels following Adrenalin plus glucagon showed twice

to a variety of factors. Cellular damage and poor nutrition with consequent inadequate supplies of liver glycogen and poor intracellular metabolism probably offer a reasonable explanation. It is unlikely that a specific deficiency of the enzyme phosphorylase plays a role here; however, our data offer no proof of this.

Glucagon definitely acts as an insulin antagonist. Our data show that insulin inactivation did not occur under the experimental conditions used.

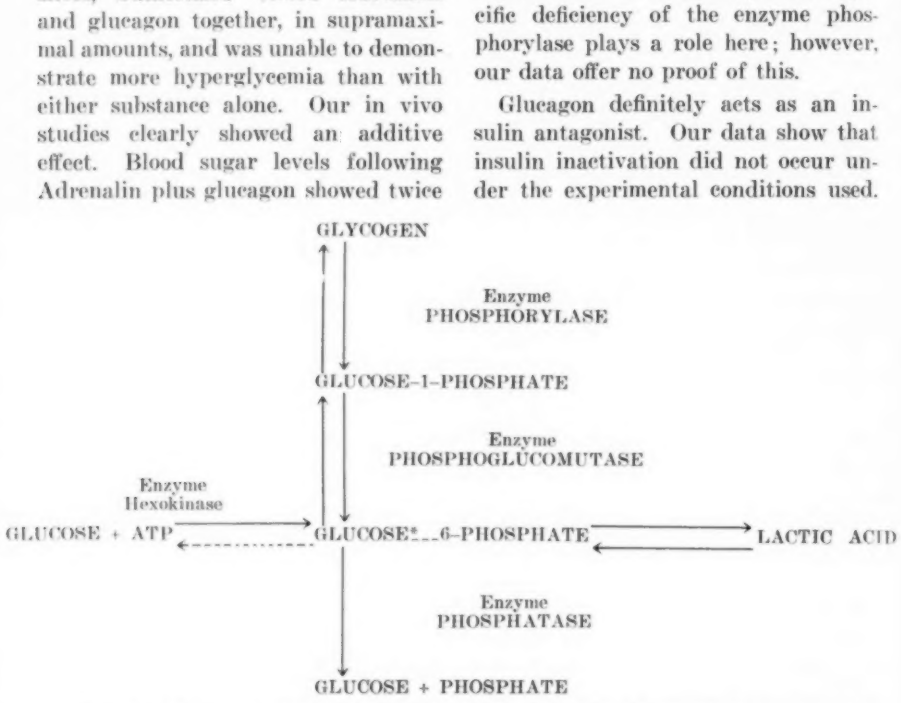

Fig. 4.—Scheme of glucose metabolism, illustrating how glycogenolysis occurs when glucagon stimulates phosphorylase activity, as shown by C. F. Cori. (The enzymatic synthesis and molecular configuration of glycogen, Carbohydrate Metabolism, The Johns Hopkins Press 1: 3, 1952.)

the increase obtained with either alone. Saturation of the enzyme system with Adrenalin or glucagon can be attained in a controlled "in vitro" technique, using supramaximal amounts. This, of course, cannot be done in the human being because of the well-known physiological effects of Adrenalin.

On the basis of theoretical considerations and the work of Kibler and associates[13] the subnormal response to glucagon of patients with extensive liver disease was expected. This may be due

With simultaneous administration of glucagon and insulin, initial hyperglycemia was followed by rapid decrease in blood sugar at the sixty-minute interval, to concentrations comparable with those resulting from insulin injection alone. The antagonism can only result, therefore, from rapid liver glycogenolysis by glucagon. Similarly, it is apparent that the drug is effective only if liver glycogen stores are adequate. In these studies, it was noted that repeated tests in the same

patients on successive days resulted in a decrease of the hyperglycemic effect of glucagon presumably due to depletion of liver glycogen. For this reason two to three days should be allowed between tests.

McQuarrie[18] has demonstrated the absence of pancreatic alpha cells in some patients with idiopathic hypoglycemia and postulated a resulting deficiency of the hyperglycemic factor. In view of this, it had been hoped that glucagon would be of therapeutic value in this disease; however, the present form is too short-acting. No cumulative effect was evident with intermittent injections every three or four hours. Continuous intravenous injections failed to maintain initial blood sugar elevation.

During acute hypoglycemic episodes, symptoms could be relieved by glucagon, and blood sugar demonstrated. This shows the availability of normal liver glycogen and the lack of a normal glycogenolytic mechanism in this disease.

Glycogen storage disease may be due to specific abnormalities in the structure of glycogen or to an enzyme deficiency.[8] In 1929, Schoenheimer[19] studied the glycogen isolated from von Gierke's original case and showed it to be normal in structure. Cori and associates[7] reported two cases with abnormal glycogen. In one, the outer chains of the glucose residues of the glycogen were very short, and in the other, they were abnormally long. In two of their cases which terminated fatally, they were able to demonstrate a specific lack of activity of glucose-6-phosphatase. In two other cases of von Gierke's disease with mild symptoms, the activity of this enzyme was diminished, whereas the enzyme was present in normal amount in two others.[7] In 1954, Schulman and Saturen[20] and Cori and Schulman[21] again confirmed the fact that glucose-6-phosphatase is diminished in liver tissue obtained from patients with this disease. Schulman and Saturen[20] also suggested that the glucagon tolerance test might be of real diagnostic value in glycogen storage disease; however, our data do not substantiate this. Cases 1, 4, and 5 showed a substantial blood sugar elevation after glucagon administration. Cases 1 and 4 showed a low Adrenalin tolerance test, but a moderate hyperglycemic response to glucagon, whereas Case 6 showed abnormal hyperglycemic response to Adrenalin but none to glucagon. Case 5 revealed a normal response to both. It would appear from these data that neither the Adrenalin nor the glucagon tolerance tests are of pathognomonic value in the diagnosis of glycogen storage disease.

SUMMARY

1. Glucagon was administered to thirty-four children varying from 2 months to 13 years of age. It consistently produced a hyperglycemic effect in normal subjects. The drug was effective intravenously and subcutaneously. Dosage over 20 μg per kilogram did not increase the hyperglycemic response.

2. The hyperglycemic effect of glucagon was increased and prolonged by simultaneous Adrenalin administration.

3. Glucagon can mobilize liver glycogen in spite of simultaneous insulin administration and is of value in controlling convulsions due to hypoglycemia.

4. Five patients with severe liver disease failed to show the normal hyperglycemic response following glu-

cagon administration. Three children with glycogen storage disease showed a similar lack of hyperglycemic response but three other cases revealed moderate increases.

5. Four patients with spontaneous hypoglycemia responded to glucagon with normal hyperglycemia.

6. A low glucagon or Adrenalin tolerance test is helpful in establishing the diagnosis of glycogen storage disease, but a normal response to either test does not rule out the diagnosis.

We are appreciative of the valuable cases of glycogen storage disease placed at our disposal by the physicians mentioned.

We also wish to thank Mildred Quiroz and Marion Worthy for their able technical assistance.

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CHOLELITHIASIS IN SICKLE CELL ANEMIA

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Houston, Texas

SINCE the original description of sickle cell anemia was made by Herrick[1] in 1910, a voluminous literature pertaining to this subject has been accumulated. The clinical and pathologic features of this disease have been reviewed extensively by many authors; however, the incidence and importance of gall bladder disease in sickle cell anemia has not been sufficiently emphasized. Such an omission is noteworthy since an exhaustive review of case reports and autopsy protocols reveals there is a significant incidence of biliary calculi in patients with sickle cell anemia. An association is not surprising since hemolysis of red blood cells is regarded as one of the causes of stone formation in the gall bladder, and excessive bilirubin as well as increased cholesterol levels in the blood, characteristic findings in chronic blood destruction, have been associated with cholelithiasis. In a report from the Mayo Clinic[2] it was found that 70 per cent of their patients with congenital hemolytic anemia had associated cholelithiasis.

The following case reports are presented as examples of gall bladder disease in patients with sickle cell anemia.

From the Department of Pediatrics, Baylor University College of Medicine; Pediatric Out-Patient Service, Jefferson Davis Hospital; and Pediatric Out-Patient Service, Hermann Hospital.

CASE REPORTS

Case 1.—M. W., a 14-year-old Negro boy, was first seen in 1944 at the age of 6 years in the outpatient service at Hermann Hospital. His foster mother, who had no knowledge of his parents, stated the diagnosis of sickle cell anemia was made on this boy at the age of 18 months. From the onset of the disease until the present admission to the hospital —twelve and one-half years—this patient had complained of recurrent leg pain, intermittent attacks of jaundice, and showed evidence of retarded growth. Although he often suffered attacks of nausea and vomiting, he experienced no frank abdominal cramping until age 8 at which time his episodes of sickle cell crisis became associated with rather severe constant abdominal pain. Subsequent to the onset of these episodes of abdominal pain the child was hospitalized and given transfusions on numerous occasions. Laboratory determinations in the interim 1944 to 1947 revealed: Icterus index varied between 4 and 27 units; hemoglobin range of 6 to 10 grams, with red blood counts of 2 to 3 million.

In April, 1952, the patient presented himself with symptoms of marked abdominal pain associated with vomiting. Because of the seriousness of the pain and its localization to the right side of the abdomen, he was admitted to the hospital for observation. Physical examination at this time revealed a thin, chronically ill child who preferred to lie on his right side with his legs flexed upon his abdomen. There was mild icterus of the scleras. Examination

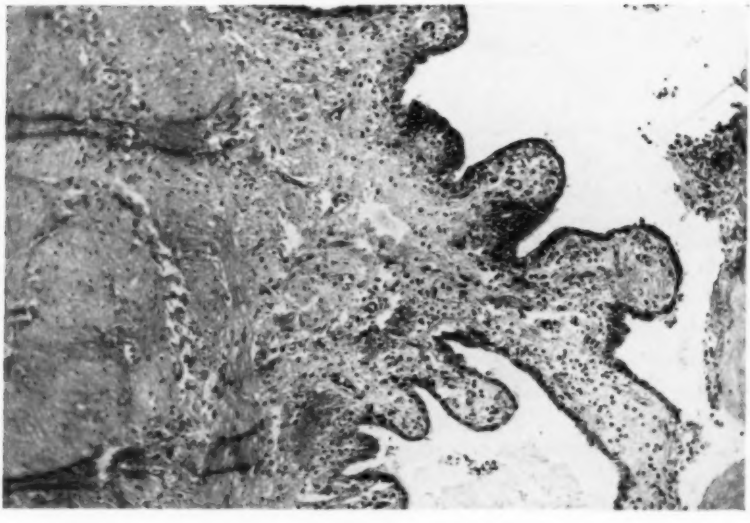

Fig. 1.

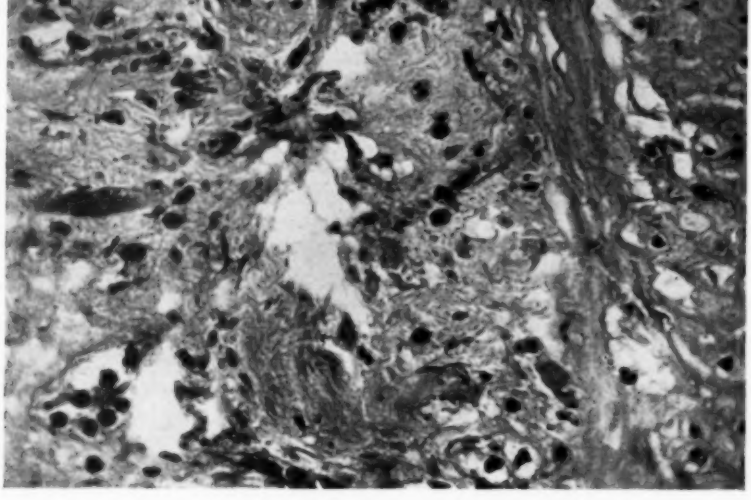

Fig. 2.

Figs. 1 and 2.—The gall bladder mucosa is well preserved and arranged in deep folds of uniformly thick columnar epithelium. There is a diffuse inflammatory cell infiltration throughout these sections, consisting predominantly of polymorphonuclear leukocytes, eosinophils, and lymphocytes. An exudate of fibrin and inflammatory cells covers many areas of the mucosal surface. The fibers of muscularis are separated by tiny slender vacuoles indicative of edema, and there are numerous dilated thin-walled blood vessels. The majority of the erythrocytes in these blood vessels are sickle-shaped and there are numerous stab forms among the neutrophils. There is one large collection of yellow pigment embedded deeply in the muscularis.

of the abdomen revealed the liver to be enlarged 6 cm. below the right costal margin. The spleen was felt 2 cm. below the left costal margin. There was marked tenderness in the right lower quadrant and mild tenderness in the right upper quadrant. Rectal examination revealed fullness and tenderness on the right side. Temperature (rectal) was 99° F.; pulse 88; respiration 24 per minute. Laboratory work revealed the following: red blood count 3 million; hemoglobin 9 grams; white blood count 19,350 with 75 per cent polymorphonuclears. Because of the acute nature of his condition and the suggestive physical findings, a surgical consultation was obtained. The surgeons concurred with the diagnosis of an acute abdomen specifically suspecting an acute appendicitis. Accordingly, operative intervention was undertaken on the evening of admission.

The abdomen was opened through a McBurney incision and the child was found to have a thickened, injected appendix which was removed without incident. Prior to closing the incision, an exploratory examination of the remainder of the abdomen was undertaken. In the right upper quadrant the surgeon encountered a tense cystic mass which upon closer inspection was found to be an edematous, dilated gall bladder. This was aspirated and white bile removed, which on culture contained gamma streptococci. After inspection of the common duct which revealed neither dilatation nor stones, the gall bladder was removed and found to contain many pigmented stones. The pathologic report of the organs removed was as follows: (1) cholecystitis, acute and chronic with cholelithiasis; (2) appendix, fibrous obliteration of the lumen. Figs. 1 and 2 represent microscopic sections of the gall bladder.

The patient had an uneventful postoperative course and was discharged on the sixth day following surgery.

Because of the extreme interest in this case he was recalled one week after discharge for complete laboratory evaluation. At this time, fourteen days after removal of the gall bladder, the following findings were reported: bilirubin, 2.7 mg. per cent; cholesterol, 108 mg. per cent; nonprotein nitrogen, 35 mg. per cent. Electrocardiogram revealed left and right ventricular hypertrophy. X-ray examination of the long bones and skull revealed changes which were stated to be compatible with those found in sickle cell anemia.

It is of interest to note there have been two admissions to the hospital subsequent to the removal of the appendix and gall bladder, and on both occasions the patient has complained of abdominal pain.

CASE 2.—B. U. T., a 10-year-old Negro boy, has been followed in the pediatric outpatient clinic at Jefferson Davis Hospital since birth. The diagnosis of sickle cell anemia was first made when the child was 4 years old. There are six siblings; only one, a female,* has sickle cell anemia. The patient has had only one episode of abdominal crisis with jaundice at age 5 and was given one transfusion at the time. Subsequently he has never required further transfusions. His only complaints in recent years have been intermittent leg pain and poor weight gain.

Examination in December, 1954, revealed a small pale child in no distress; height 53 inches, weight 54 pounds. The blood pressure was 110/65. There was cardiomegaly with the left border of the heart 8 cm. to the left of the mid-sternal line. There was a grade 3 systolic murmur heard over the entire precordium and a grade 2 diastolic murmur heard only at the apex. The liver was palpable 4 cm. below the right costal margin; the spleen was not palpable.

Laboratory findings in December, 1954, revealed: red blood count, 3

*L. B. T., a 12-year-old Negro female, was included in the gall bladder study cases and found to be free of calculi.

million; hemoglobin, 7 grams; sickle cell preparation demonstrated 80 per cent sickling; serum bilirubin, 1.4 mg. per cent; cholesterol, 138 mg. per cent. Roentgenographic examination of long bones and skull were reported as compatible with the diagnosis of sickle cell anemia. Oral cholecystographic examination demonstrated calcified opacity in the gall bladder (Fig. 3). Electrocardiogram revealed a normal tracing.

The occurrence of biliary calculi in this child was demonstrated only as a result of routine gall bladder studies initiated in this clinic on all diagnosed sickle cell anemia patients.

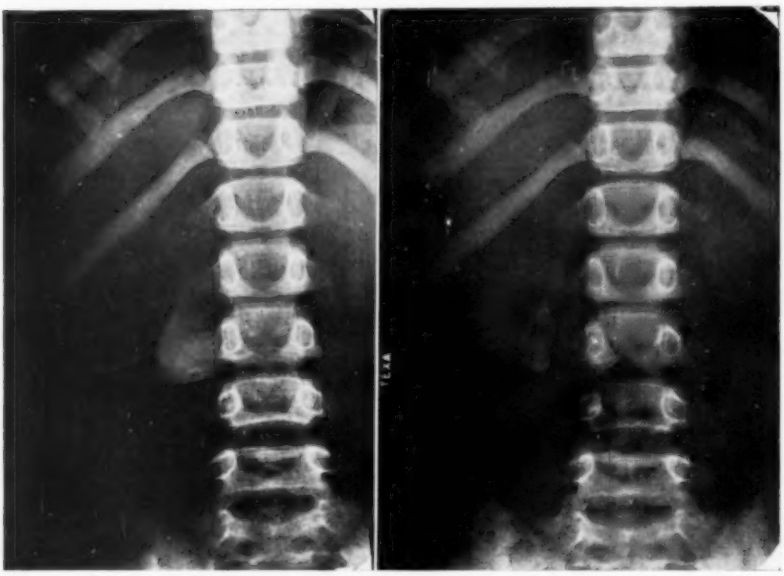

Fig. 3.

DISCUSSION

Pathogenesis of Biliary Calculi.—Increased red blood cell destruction is a characteristic feature of sickle cell anemia. On disintegration of the red blood cell, bilirubin is formed from the hemoglobin liberated. This phenomenon is seen in all hemolytic anemias. It is believed this excess of bilirubin favors aseptic precipitation of pigment in the biliary tract with resultant stone formation. Stasis from obstruction and/or infection are important contributing factors.

Incidence of Cholelithiasis.—The number of autopsy reports of sickle cell anemia is comparatively small. Weens[3] reports forty-four protocols of patients with sickle cell anemia. He found twelve of these patients had cholelithiasis. Table I from Weens[3] reviews the ages of these patients as compared with the general incidence of cholelithiasis in the Negro as reported by Jaffe.[4] From this table it will be seen that cholelithiasis was not encountered during the first decade of life. Gallstones were observed, however, in patients who died in the second decade, and were

quite common in the third and fourth decades. There were no stones in the patients beyond the age of 40 years. Comparing this with the data from Jaffe[4] one finds the over-all incidence of stones in the Negro is more common beyond the age of 40. From this the conclusion may be drawn that occurrence of cholelithiasis in a Negro below the age of 40 years should suggest the probable diagnosis of sickle cell anemia.

The aforementioned statistical evaluation by Weens[3] was of autopsied cases. This stimulated efforts on our part to conduct a clinical evaluation on the incidence of cholelithiasis in the sickle cell anemia patients being followed by the pediatric services in the two major hospitals in this city caring for Negro patients.

Method.—An attempt was made to evaluate the sickle cell patients in the pediatric age group being fol-

TABLE I*

TOTAL NUMBER OF AUTOPSY CASES					NUMBER OF PATIENTS WITH CHOLELITHIASIS			GENERAL INCIDENCE OF CHOLELITHIASIS IN NEGROES (JAFFE)	
AGE	MALE	FEMALE	SEX NOT GIVEN	TOTAL	MALE	FEMALE	TOTAL	MALE %	FEMALE %
0-10	6	6		12				0.0	0.0
11-20	2	6	1	9	1	1	2	0.0	0.0
21-30	8	5		13	4	1	5	0.0	3.28
31-40	3	2		5	3	2	5	0.73	7.50
41-50	1	2		3				0.0	12.24
51-60								1.86	16.27
61-70		1		1				4.34	25.00
Above 70		1		1				6.66	20.00
Total	20	23	1	44	8	4	12	1.04	10.23

*From Weens.[3]

TABLE II

NAME	AGE (YR.)	SEX	BILIRUBIN MG. %	CHOLESTEROL MG. %	CHOLECYSTOGRAM
L. H.	3½	M	1.0		No stones
H. C.	4½	M			Questionable stone
C. M.	5	M	3.9	175	No stones
T. G.	5	M	6.0	178	No stones
T. W. H.	5	M			No stones
L. E.	6	M	2.1	181	No stones
L. W.	6	M	1.2	169	No stones
T. C.	6½	M	0.2		No stones
J. L. J.	7	M	1.2	149	No stones
V. C. P.	7	M	1.6	186	No stones
R. W.	8	M			No stones
A. S.	9	F	6.6	171	No stones
F. C. S.	9	M	4.1	154	No stones
D. F. W.	9	F	4.4		No stones
B. U. T.	10	M	1.2	170	Two calcified stones
I. J. H.	10	F	2.7		Nonvisualization
D. J. W.	11	F			No stones
K. J.	11	M	3.9	117	No stones
L. B. T.	12	F	0.9	170	No stones
R. G.	16	M	4.0	162	No stones
M. W.	16	M	2.7	108	Surgically removed stones

lowed in the clinics at Jefferson Davis Hospital and Hermann Hospital. Forty-eight patients were contacted, of which twenty-one reported for examination. Oral cholecystograms were performed using 3-(3-amino-2, 4, 6-tri-iodophenyl)-2-ethyl-propanoic acid,* 0.5 Gm. tablets, in dosage of 50 mg. per kilogram of body weight. In the majority of cases, simultaneous evaluation of serum bilirubin and cholesterol was included. (See Table II.)

Results.—Visualization of the gall bladder was obtained in all but one patient. Of the twenty-one patients, two had stones, an incidence of 9.5 per cent. For the corresponding age group (0 to 20 years), Weens[3] reported a similar incidence of two in twenty-one cases or 9.5 per cent. We can therefore duplicate the autopsy incidence by this clinical evaluation.

Cholecystography in Children.—Harris and Caffey[5] reported cholecystography in children under 3 years of age as an unsatisfactory procedure; however, in age group 3 and above, uniformly good results can be obtained. Hrdlicka and associates[6] established the nontoxic dosage of Telepaque to be 150 mg. per kilogram of body weight and this dosage was used in the study by Harris and Caffey.[5] In the present study a much smaller dosage was successfully employed. Patients examined at the Hermann Hospital were given a mixture of egg yolk, glycerine, and lecithin* to facilitate emptying of the gall bladder.

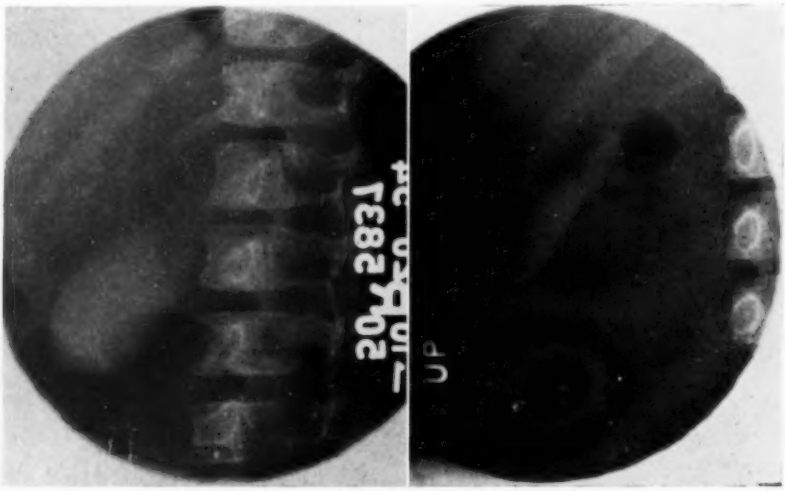

Fig. 4.

Ten patients were examined in this manner and function was obtained in every case. Fig. 4 is an example of such a patient with good function.

Cholelithiasis and Abdominal Crisis.—Episodes of abdominal pain, fever and leukocytosis occur frequently in sickle cell disease, and such an attack must be distinguished from an acute abdominal condition. The

*Telepaque, Winthrop-Stearns, Inc.

*Cholex, Bell Craig, Inc.

literature reveals many patients with sickle cell anemia who have been operated upon for appendicitis, cholecystitis, and ruptured peptic ulcer.

As yet the cause of this crisis in sickle cell anemia is unsolved. Hepatic and mesenteric infarcts, splenic hemorrhage, and nerve root pain due to changes in the vertebral bodies have been suggested. Primary biliary disease seems unlikely since not all sickle cell patients have stones in their gall bladders, and even after cholecystectomy where stones are present, the patient frequently continues to suffer from abdominal crisis. However, one must be cognizant of the association of episodes of abdominal pain with true biliary colic in patients with sickle cell anemia.

SUMMARY

Two cases of cholelithiasis in patients with sickle cell anemia have been presented.

Twenty patients in the pediatric age group with sickle cell anemia were examined with oral cholecystograms to determine the incidence of detectable biliary calculi. This technique was responsible for the diagnosis of cholelithiasis in two patients in this study.

Review of the literature with respect to biliary calculi in the Negro in general and specifically in sickle cell anemia is included.

We wish to express appreciation for the x-ray interpretations by Dr. L. M. Vaughan, head of Department of Radiology, Hermann Hospital, and Dr. V. P. Collins, head of Department of Radiology, Jefferson Davis Hospital.

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Forecasting the Atomic Age

Gravestone inscription in Worcester, Massachusetts.

In Memory of Charles, Son of Mr. Joseph & Mrs. Mary Blair
who died May ye 28th 1775 in the 24th year of his age
Time shall be slain, all nature destroy'd
Nor leave an atom in the mighty void.

EPIDEMIC GASTROENTERITIS DUE TO ESCHERICHIA COLI 0-111

A Review of the Literature, With the Epidemiology, Bacteriology, and Clinical Findings of a Large Outbreak

W. Dean Belnap, Captain, MC, USA, and John J. O'Donnell, MC, USA

DURING the past two decades the medical literature throughout Europe has discussed the association of special serological types of *Escherichia coli* with epidemic diarrhea of the newborn and of infants. The same organism has been known to occur in more recent outbreaks in this country.[1-3] To date, there have been few accounts that discuss the clinical and pathological aspects of the associated gastroenteritis.[5, 6, 44]

Several authors who have incriminated pathogenic strains of *E. coli* as causal agents of gastroenteritis have also been careful to point out that the possibility of a viral agent had not been excluded. In fact, with the exception of a report by Taylor and associates[7] in which attempts were made to recover a virus, no authors reporting the isolation of this bacterium have ruled out a viral etiology. A symbiotic relationship between *E. coli* and a viral agent has also not been excluded.

The present discussion is directed first toward a brief review of the literature in support of the impression of a causal relationship between certain strains of *E. coli* and diarrhea. Second, we wish to lend our experience with an epidemic of gastroenteritis occurring in northern Virginia from October, 1953, through February, 1954.

In 1927 Adam[8] concluded that a special type of *Bacterium coli*, biochemically unique in its fermentation properties, was found regularly in the feces of infants with gastroenteritis. Adam's observations were later confirmed by Cziglany[9] during an epidemic in Budapest. In 1948 Bray and Beavan,[10] in Great Britain, published a work on a series of fifty-one cases, in over 90 per cent of which he recovered a serologically homogenous type of *E. coli* which he called *Bacterium coli neapolitanum*.

Improved techniques enabled Kaufman and Dupont[11] in 1947 to reinvestigate the immunology of colon bacilli. Largely through their efforts, a scheme has developed whereby *E. coli* strains are classified according to their antigenic properties. Their identification is based upon the presence of different O, K, or H antigens representing, respectively, somatic, capsular, or flagellar moiety. The vast majority of reports in the literature have incriminated a strain with the number 111 type of somatic antigen and the *B-4* variety of capsular antigen.* Less frequently observed is

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**Escherichia coli 0-111 B-4* has been called *Bacterium coli* var. *neapolitanum*, *B. coli alpha*; *B. coli D 433*; *B. coli B.G.T.*

the strain with the number 55 type of somatic antigen.*

There are already many references in the literature which help confirm the relationship between *E. coli 0-111 B-4* and gastroenteritis.

Several workers[3, 5, 6, 11, 12, 13, 44] have found the organism in nearly pure culture in the absence of known pathogens. Giles and associates[6] were able to demonstrate the *0-111* strain in 94.7 per cent of 417 cases of gastroenteritis in Aberdeen during 1947. Only 3.7 per cent showed positive culture in a series of 208 cases of so-called parenteral diarrhea. Seven hundred eight healthy infant and adult controls revealed the low incidence of 1.8 per cent positive cultures. Other authors[6, 13-18] have found the presumed pathogenic strains in only a small percentage of healthy adults and children. During the convalescent period of the disease, the organism has been gradually replaced by normal intestinal flora.[14]

Rising agglutinin titers for *E. coli 0-111* have been found in the serums of infants recovering from a bout of epidemic diarrhea.[5] Laurell and co-workers[12] report a case with an antibody titer against the *0-111* strain rising from 1:32 to 1:320. Giles and associates[6] found twenty-one patients in their series of forty-one with titers as high as 1:640. A series of controls revealed an insignificant titer in all samples.

It is of particular interest that some workers have found the organism to be present in the respiratory tract associated with signs and symptoms of a respiratory infection as well as those of gastroenteritis.[4, 12] According to Laurell and co-workers,[15] patients with *E. coli 0-111* in the nose most easily spread the infection to their surroundings. When these organisms are found in the respiratory tract, they behave like other bacteria in this environment.

The organism appears to be highly sensitive to chloramphenicol and neomycin[12, 13, 15, 16, 17, 18, 44, 45] and variably sensitive to chlorotetracycline[12, 16] and oxytetracycline,[17] both in vivo and in vitro. Recovery corresponds to disappearance of the organism from the stools. Penicillin, streptomycin, and the sulfonamides[6, 12, 17] appear to be ineffective clinically and in vitro.

Neter and collaborators[4] were able to reproduce the disease in a "non-diarrheal" infant fed *E. coli 0-111*. After only twenty-four hours the infant began to have symptoms of gastritis and then in forty-eight hours diarrhea, with the organism being cultured in the vomitus, nasopharynx, and stools. Treatment with oxytetracycline resulted in clinical improvement and the disappearance of the organism within twenty-four hours. Neter and associates have also developed a sensitive hemagglutination test for the demonstration of antibodies to *E. coli 0-111, 0-55,* and *0-26* and have shown that adult volunteers develop an increased specific hemagglutination titer of antibodies to *E. coli 0-111, 0-55* and *0-26* following feeding experiments.

HISTORY OF THE EPIDEMIC

According to the U. S. Public Health Service,[19] a generalized east coast epidemic of gastroenteritis began in the Carolina states during September, 1953. As the disease spread from place to place it would reach its

E. coli 0-55 has also been called *B. coli beta.*

peak incidence in the population about six weeks after its first appearance. Spreading by geometric increment, the disease moved northward, not involving the New England states until March, 1954. As it spread, explosive outbreaks were limited to institutions, hospital wards, and newborn nurseries. The epidemiological characteristics were rather that of a respiratory-borne infection. It is of particular interest, especially when the communicability is under consideration, that workers[12, 15, 20] with *E. coli 0-111 B-4* have often found the organism present in the respiratory tract. Laurell and co-workers[12, 15] have shown that these coliform bacteria occur commonly in the respiratory tract of young infants and that they are often present in the nose. His study of hospital environment provided evidence in support of an air-borne type of dissemination.

The U. S. Army Hospital at Fort Belvoir serves a large area of northeastern Virginia and serves an Armed Forces population of about 30,000 including dependents. As shown in Fig. 1, the disease first made a significant appearance in this area during late October, 1953, reaching its peak in mid-December, 1953, and disappearing during February, 1954.

The peak shown during the second week in January, 1954, was due to a sudden outbreak in the newborn nursery. Two mothers admitted to the obstetrical service with a history and active infection clinically characteristic of the disease were the probable source of the organism. The mild form of the disease in adults apparently failed to motivate their volunteering information until after more thorough questioning. Thirteen of eighty-eight full-term babies in the nursery, during a five-day period, contracted the disease on the third to sixth day of life. All thirteen were in the nursery during the same three-day period the two mothers were convalescing. Two premature infants simultaneously developed the infection. Formula preparation was carefully checked and found to be free of apparent error. The outbreak was limited by closing temporarily the old nursery and bringing in new personnel for the new babies. None of the breast-fed infants showed signs of the illness. This pattern is compatible with the experience of others[4-6, 12, 21, 22] in which a significantly low incidence of *E. coli 0-111 B-4* gastroenteritis was found among the breast-fed infants as compared with those fed formula. In a study of over 300 cases, Alexander[21] found that 94.0 per cent of his infants were not breast-fed. Giles[6] cited only four fed mother's milk in a series of 207 cases, of which 94.7 per cent had positive cultures for *E. coli 0-111 B-4*.

The last small peak occurring during the first week in February, 1954, as shown in Fig. 1 represents the cross-infection on the hospital ward. Six patients hospitalized for illnesses other than gastroenteritis developed the disease within a few days of each other. They had all been on the pediatric service for at least the previous week and two for as long as three weeks. There were two additional examples of cross-infection occurring at other times during the epidemic. From each of the eight, *E. coli 0-111 B-4* was recovered, and a rising antibody titer was noted in the seven survivors during convalescence. All of the fifty-one hospitalized patients

were under 2 years of age. Of these, forty-eight were less than one year old and thirty-seven, or 73.0 per cent, were under 6 months of age.

With increasing age of patient, the disease became less severe. A study of 142 patients up to 12 years of age treated in the pediatric outpatient clinic revealed 83.5 per cent to be over one year of age and 89.0 per cent over 6 months of age. Lyon and Folsom[23] described a concurrent mild "adult type" of infection in the epidemic they observed. Other workers[4, 6, 12] found the vast majority of their hospitalized and fatal cases to be under 6 months of age.

As regards sex, males were affected more frequently than females, but the difference was not so striking as in the fatalities. Eight of the fifty-one hospitalized patients and one infant contracting the disease shortly after discharge from the newborn nursery died at home. The over-all mortality for hospitalized cases was 15.7 per cent but for those in the neonatal period, 40.0 per cent. The very high mortality rate attests to the virulence of the organism. Similar experience with *0-111* and *0-55* strains as reported gives mortality figures ranging from 28 to 83 per cent, with an average of 50.6 per cent.[1, 3, 5, 12, 13, 18]

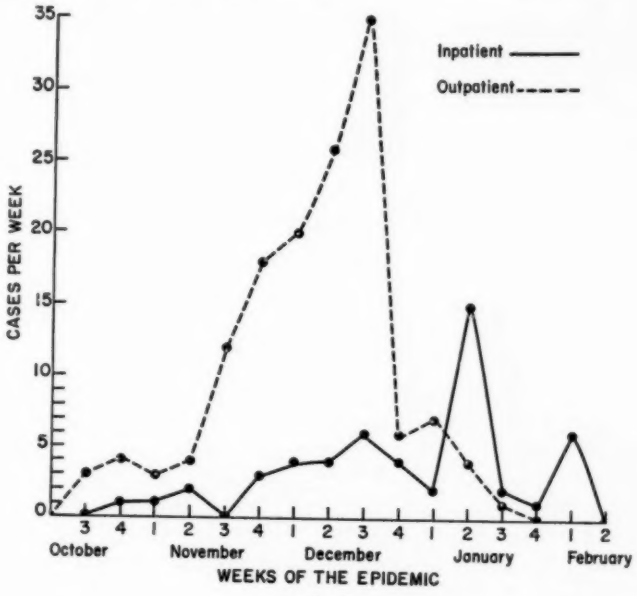

Fig. 1.

BACTERIOLOGY AND VIROLOGY

After routine bacteriological investigation failed to demonstrate the presence of any well-known enteric pathogens in the first cases seen during the epidemic, special attention was paid to a possible virus or coliform etiology. A number of workers have suggested the possibility of a virus in the causation of gastroenteritis. Barenburg and associates[24] found

in some fatal cases of diarrhea mononuclear lung infiltrations suggestive of a virus infection. Lembke and coworkers[25] and others identified a filtrable agent lethal to mice in the stools of infected infants. Light and Hodes[26] isolated a filter-passing agent in epidemic diarrhea, which, in turn, regularly produced diarrhea in calves. These results were confirmed by Buddingh and Dodd[27] and, in addition, produced keratitis in experimental animals. Christensen and Biering-Sorensen[28] were of the opinion that round cell infiltration of the brain in infants dying of gastroenteritis represented changes due to an encephalotropic virus. Pappenheimer and Enders[29] demonstrated inclusion bodies in the cells of intestinal mucosa in enteritis cases.

Routine bacteriological cultures taken during the Belvoir outbreak did not reveal any enteric pathogens. The coliform flora was then observed in detail at the Army Medical Service Graduate School, and the presence of *E. coli 0-111 B-4* in stools of acutely ill infants was recognized. In eight cases, the organism was present in almost pure culture. It was also isolated from vomitus of three patients. Three of five cases on whom paired serum specimens were obtained showed appearance of an agglutinin for the *0-111* antigen during the illness; twelve more late serum samples showed titers of from 1:20 to 1:320. Control serums from healthy adults and infants did not contain comparable agglutinins. Out of ten cases cultured during the convalescent stage, one continued to excrete the organism during four months after the acute phase had passed. The pediatric staff and ward personnel were cultured late in the epidemic; two of thirty-six staff members were found to be carrying the organism.

Virus isolation attempts were carried out in detail. The results, using embryonated eggs, mice (young and suckling), young hamsters, and rabbits, were negative for recovery of a filtrable or cytopathogenic agent.

A detailed discussion of the methodology and results of the virus, bacterial and serological studies is the subject of another paper participated in by one of us (W. D. B.).[30]

CLINICAL FINDINGS

The incubation period in epidemics associated with *E. coli 0-111 B-4* has not been determined with certainty, either in institutional outbreaks or among those in the general population. In our own experience it was often difficult to ascertain exactly when an infant started to develop the disease. Patients were not usually seen until after symptoms of gastritis had commenced. They did, however, frequently present a history of a respiratory illness of indefinite length preceding the gastritis. Laurell[12] has found the respiratory phase of the illness to be highly communicable. One paper concludes that the incubation period may be as long as twenty-three days,[12] while another states as short as two days.[4] Other estimates range within those limits.[5, 6, 13]

In the nursery outbreak, however, the incubation period had to be as short as four days or less since definite symptoms were present on the fourth day of life in most newborn infants. Six cases of cross-infection on the pediatric ward followed mass hospitalization of the newborn infants by two weeks. Two of these in-

fants had been on the ward for the latter week, whereas the other four had been hospitalized at least the full two weeks. Neter's infant case, as previously mentioned, developed signs and symptoms of gastroenteritis twenty-four hours after ingestion of *E. coli 0-111 B-4*. His several adult volunteers developed symptoms after approximately the same period. One might speculate that the incubation period is a quantitative function of exposure.

The slow and low-grade onset of the disease was certainly not an indication of the ultimate extreme toxicity, severe diarrhea, periodic circulatory collapse, and notably prolonged course. The clinical pattern does not appear to have differed markedly from the brief descriptions of others acquainted with similar epidemics. The average length of illness was thirty-seven days among the survivors, with symptoms lasting forty-nine days in one. Excluding the infant dying at home, the infants survived an average of twenty days.

The first signs and symptoms to appear were those associated with mild injection of the nasopharynx. Vomiting would usually precede the onset of diarrhea by twenty-four to thirty-six hours. Stools would first be loose, then watery, with the severity of diarrhea gradually increasing to the seventh day. Until terminally, the stools contained neither mucus nor blood.

During periods of profuse watery diarrhea, the infants would lose as much as 15.0 per cent of their body weight. Such episodes would produce hyperelectrolytemia and severe shock, with mottled cyanosis and signs of central nervous system disturbance. The average patient would have three to four such episodes before complete recovery was achieved.

Several authors[4-6, 12, 13, 18, 23, 31] working with epidemics of *E. coli 0-111 B-4* describe a clinical picture with frequent cerebral phenomena indistinguishable from the pattern associated with hypertonic dehydration. Symptoms referable to the central nervous system, ranging from marked irritability with muscular hypertonicity to severe convulsions and coma, were discussed. No mention was made as to the appearance of these manifestations in the time sequence of the disease nor was any attempt made to rule out hypernatremia as a cause. Rather than suggesting a hypothesis of neurotropism of the organism, as do the above-mentioned authors, our experience leads us to agree with Finberg and Harrison[32] and Weil and Wallace[33] in attributing the syndrome to a disturbed fluid and electrolyte balance. With severe relapses of diarrhea the accumulative cation of the blood would often be greater than 170 meq. per liter.

Each episode would require a new program for fluid and electrolyte repair. Hypocalcemia would often develop during the period of rehydration necessitating the intravenous injection of calcium gluconate solution. The numerous relapses of severe diarrhea were independent of the oral and the fluid and electrolyte replacement schedule. Water loss in the stools apparently exceeded salt loss. Chloride was retained in greater quantities than sodium. Blood chemistries for the sodium, potassium,

carbon-dioxide combining power, and chloride levels revealed a constant tendency toward hyperelectrolytemia and particularly hyperchloremia. Alkaline repair solutions usually containing no more than 45 meq. per liter of sodium were required to maintain normal electrolyte composition of the blood. Day after day the fluid requirements seldom dropped below 300 c.c. per kilogram per day. During the severe relapses of diarrhea the requirement often rose to 500 c.c. per kilogram per day. The loss of potassium did not appear to exceed that of sodium and no more than 3.0 meq. per kilogram per day was required to maintain a normal blood level.

During the first days of the disease the white blood count would often rise to from 20,000 to 30,000 with 70.0 to 80.0 per cent lymphocytes. As the disease progressed there would be a reversal, with a preponderance of polymorphonuclear leukocytes.

One of the most distressing aspects of the disease was the associated periodic circulatory collapse present even though fluid and electrolyte balance was in a state of near normalcy. During such occasions the infant would become apathetic, irresponsive, and the skin would be cold and moist and show signs of mottling. These findings were distinct from those associated with hyperelectrolytemia and depletion of the extracellular fluid. The experience of some authors[34-37] using adrenal cortical hormone during similar episodes encountered in gastroenteritis encouraged clinical trial of these materials. Without regard to fluid and electrolyte replacement therapy, the infant would often show improved sensorium and circulation in less than one hour. Adrenal cortical extract in dosages of 2.5 c.c. per kilogram and cortisone 6.25 mg. per kilogram were used as often as every four hours.

The temporary response to adrenal hormone therapy stimulated further study as to the possibility of adrenal insufficiency resulting from the severe and prolonged stress of the illness. The eosinophil count is a reliable guide to the status of adrenal function. The following case produced some interesting findings.

J. G., a 6-month-old white male, was admitted to the pediatric service with a history of thirty-six hours of vomiting five days before admission, followed by progressively more severe diarrhea. The clinical and laboratory picture was compatible with hyperosmolarity of the extracellular space. (See Table I.) Fluid and electrolyte correction was achieved within twenty-four hours, and he was maintained first on oral electrolyte solutions, then milk feedings for the next six days. A relapse of diarrhea was accompanied by a weight loss of 720 grams in twenty-four hours, with repetition of hypertonic dehydration. After the second correction it was found that satisfactory balance was maintained with a minimum of 250 c.c. fluid per kilogram per day. The constant, moderately severe diarrhea was not altered by starvation or variation of the oral regimen. Periodically he would show signs of marked listlessness, anorexia, and vomiting. On one such occasion, his blood potassium was 4.5 meq., but the eosinophil count was 1,200 in a total white blood count of 13,500.

Coincident measurements of blood chemistries are shown in Table I. Ten cubic centimeters of adrenal cortical extract administered intravenously was followed by disappearance of

symptoms and a fall of the eosinophil count to zero. Another repetition of this experience occurred one week later. Recovery with disappearance of *E. coli 0-111 B-4* from the stools came forty-six days after the onset of symptoms.

Electrolyte determinations also lent support to the possibility of adrenal hypofunction. The next case is illustrative.

W. W., aged 7 months, was admitted to the pediatric service on Dec. 21, 1953, because of vomiting and diarrhea for four days. He first became ill two weeks earlier with similar symptoms which had cleared completely on four to five days of dietary regulation and undetermined medication.

Examination revealed a well-developed but dehydrated and acutely ill white infant who was listless, irritable, and slightly dusky in color. Rectal temperature was 102.4° F. and his weight was 14 pounds 11 ounces. A recent previous weight was 17 pounds 12 ounces. Other than dehydration, there were no abnormal findings.

Laboratory data: Urinalyses during the hospitalization were negative until January 6, except for an occasional 1 plus acetone, positive diacetic acid reaction, and frequent 4 plus sugar, the last probably due to parenteral fluid therapy. On January 6 the urine contained 15 to 20 white blood cells, and 7 or 8 fine granular casts per high-power field; cultures were negative. Table II lists the hematological findings.

Cerebral fluid on December 25 contained 2 neutrophils; sugar 90.0 mg. per cent; chloride 118.0 meq. per liter; protein was not done. Chest x-rays made on December 21 and January 12 and PPD No. 1 were negative.

TABLE I

DATE	CO_2 MEQ.	Cl MEQ.	Na + MEQ.	K + MEQ.	EOSINOPHIL	WBC
Dec. 26	16.5	128				
Dec. 27	21.0	114				
Dec. 28	25.5	102				
Jan. 4	14.4	136	166			
Jan. 11	19.0	108	143	4.5	1,200	13,500
Jan. 11					0	
Jan. 18	19.6	97	141	4.2	1,150	12,200
Jan. 19					0	

TABLE II. HEMATOLOGY

DATE	RBC	HB	Hct	ESR	WBC	PMN	LYM.	EOS.	MONO.	STAB
Dec. 21		13.8	42	12	7,300	32	66		2	2
Dec. 22		12.0	40		10,950	46	52	1	1	5
Dec. 24		12.9			7,200	48	49		3	10
Dec. 31	4,200,000	10.2	35		10,600	46	47	6	1	3
Jan. 2		12.0	39		7,900	66	29	3	1	1
Jan. 6	3,650,000	11.1			16,000	79	20		1	
Jan. 8	4,300,000	13.5	37		12,000	64	35		1	

Hospital course: On admission the patient was allowed glucose water by mouth and was hydrated parenterally with a mixture of lactate-Ringer's solution and 5 per cent dextrose in water in about 2:1 proportions, respectively. A total of 560 c.c. was given intravenously and subcutaneously. The patient appeared much improved the following day with a normal temperature and a weight gain of 12 ounces. Because of clinical improvement he was allowed boiled skim milk, and no parenteral fluids were given. But, despite only four stools, no emeses, and an ade-

quate oral intake the patient lost 14 ounces during the next twenty-four hours. Parenteral hydration was again required on the third day with considerable improvement. The same cycle occurred, and the patient was rehydrated on the fifth day. At that time the patient was placed on penicillin and streptomycin, although no signs of parenteral infection appeared. Temperature elevations accompanied each episode of acute dehydration. Water loss in the stools did not appear to be voluminous but acute dehydration occurred every other day in spite of intensive parenteral fluid therapy. By December 29 there was concern over the possibility of adrenal insufficiency due to excessive stress. The chemistries of December 30 and 31 as shown in Table III seemed consistent with this. There was a corresponding rise in the eosinophil count.

Table III. Blood Chemistries

DATE	CO_2 MEQ.	cl MEQ.	Na + MEQ.	K + MEQ.	SUGAR MG. %	BUN MG. %
Dec. 21	20	93				
Dec. 22	27	96				
Dec. 24	21	112				
Dec. 28	32	128				
Dec. 30	22.5	84				
Dec. 31	17.6	97	125	4.3		11
Jan. 2 A.M.	27	112	141	5.2	136	
Jan. 2 P.M.	23.3	104				
Jan. 3	23.9	112			72	
Jan. 4	26	125	148	5.0		
Jan. 6 A.M.	10.6	152	165	6.8		21
Jan. 6 P.M.	11	90	155			
Jan. 7 A.M.	18.5	135	154	3.5		22
Jan. 7 P.M.	18.5	134				
Jan. 8		97				
Jan. 9	27.8	101				
Jan. 11	30.2	97	135	5.5		

The patient was then put on added salt and on cortisone 12.5 mg. every six hours. He seemed to improve on this regimen, but his electrolytes were concentrated on January 4 and the cortisone dose was halved. He continued to improve until January 6, when his weight dropped 2 pounds in twenty-four hours. Because of our dependence upon frequent and urgent complete electrolyte studies and the lack of facilities at the time for cation determinations at our installation, the patient was transferred to Walter Reed Army Hospital on Jan. 6, 1954.*

Clinical and laboratory examination at Walter Reed revealed once again a picture of hypertonic dehydration. The patient was started on penicillin and streptomycin, placed on nothing by mouth for two days, and given continuous intravenous fluid replacement for five days. The hyperelectrolytemia was corrected by January 10. On the fourth day a generalized clonic convulsion of undetermined etiology responded to phenobarbital. Moderate bronchopneumonia that developed during hospitalization disappeared by the ninth day and the patient was discharged on the tenth day, or thirty-four days after the first onset of symptoms.

Many of the infants showed severe ileus that could not be attributed to hypokalemia since serum potassium determinations were normal. One case developed the serious complication of volvulus of the ileum following several days of distention.

G. P., a 2-month-old Negro female, was admitted to the pediatric

*Summarized with permission of Lt. Col. Ogden C. Burton, Walter Reed Army Hospital.

service Dec. 27, 1953, for severe weeping eczema. Following a program of conservative management, the rash had cleared and she was ready for discharge Jan. 11, 1954. On the day of discharge symptoms of gastritis commenced and during the next week she gradually developed severe gastroenteritis. The period of immediate fluid and electrolyte correction was followed by persistence of mild diarrhea and moderate apathy for the next two weeks. Marked ileus accompanied a relapse of diarrhea even though hydration and electrolytes were corrected. After five days of distention, refractory to decompression by rectal suction, she became even more acutely distended, developed high-pitched bowel sounds and spiked a temperature to 105° F. rectally. A picture of intestinal obstruction was demonstrated by x-ray. After two days of Wangensteen suction and preparatory transfusions, operation was performed and two feet of gangrenous bowel removed from a volvulus of the ileum. Postoperative recovery was surprisingly good in spite of the problems of electrolyte balance secondary to loss from both Wangensteen suction and diarrhea. Preoperatively and postoperatively the serum potassium was 4.5 to 5.0 meq. on four separate occasions. Two electrocardiograms were normal. Bronchopneumonia developed on the seventh postoperative day, and the patient died on the ninth postoperative day. At post mortem the findings, in addition to those of the other fatalities, consisted of an overwhelming pneumonia typical of *Monilia albicans* and monilial abscesses were found in several body organs from which *C. albicans* was grown. *E. coli 0-111 B-4* was cultured from the stools and urine on several occasions during the patient's hospital course.

The most interest-provocataive aspect of the entire epidemic was the terminal clinical picture and pathological findings of the eight other fatalities including the patient who was dead at the time of arrival. On an average of the nineteenth day, and immediately following an exacerbation of diarrheal symptoms and fever, these infants would show a picture of severe shock. The only time any of the cases demonstrated blood loss from the gastrointestinal tract was at this point. Emesis of "coffee-ground" material and the passing of many grossly bloody stools were a terminal finding in all cases. Each patient (except J. P.) also developed renal shutdown as determined by anuria in the last twenty-four hours of life. Coma was present during the same interval with severe and frequent convulsions in one infant. Blood loss in some instances was severe enough to require transfusion. Electrolyte balance and state of hydration were not markedly disturbed. This was maintained to the end by giving only 5 per cent dextrose in water because of the anuria.

In their last twelve hours, three of the infants began to show petechiae all over the body. Many of these coalesced to form large purpuric areas. Cultures from these areas were negative for bacteria. Numerous blood cultures taken at this time, at post mortem, and at all other times in both survivors and fatal cases were negative. Every fatal case had had heavy growth of *E. coli 0-111* in the stools and five had at least on one occasion near-pure culture of the organism. There were no abnormalities auscultated in the lungs although terminal dyspnea was severe.

All cases examined post mortem showed a gross and microscopic picture strikingly similar to that of the generalized Shwartzman reaction. Details of the pathological findings in correlation with the clinical picture is the subject of another paper.[48]

At autopsy the most consistent gross findings consisted of emaciation, occasional skin petechiae, distention and dilatation of the small bowel, a diffuse congestion and edema of the mucosal surface of the gastrointestinal tract, and focal small areas of hemorrhage and ulceration in the

small and large intestines. Microscopically, the disease presented itself as a diffuse inflammation of the mucosa of the small and large intestine, with a tendency toward excess mucous production. The superficial epithelium was missing in many areas. The connective tissue of the plicae was edematous and infiltrated with lymphocytes, plasma cells, macrophages, eosinophils, and polymorphonuclear neutrophils. In some areas there were focal areas of hemorrhage and necrosis. In these regions the capillaries of the mucosal plicae were dilated, packed with red cells, and a few contained fibrin thrombi. The connective tissue was packed with extravasated red blood cells and the glandular tissue was necrotic with a complete loss of histological and cytological architecture. Atrophy of the thymic cortex was a constant feature.

The most outstanding pathological change in the majority of the cases was intravascular fibrin thrombosis of the capillary and precapillary arterioles in the lungs, liver, brain, spleen, adrenals, and kidneys. Perivascular infiltration with polymorphonuclear leukocytes and macrophages, as well as intravascular accumulations of these cells, were prominent in the brain, spleen, and lung. The amount of thrombosis varied from one case to the next, but in the more severely involved kidneys, every glomerular tuft was completely occluded by a fibrin thrombus.

This renal lesion is identical to those in the kidney of rabbits subjected to the generalized Shwartzman reaction.[49] Thomas[50] has demonstrated that fibrin deposits in this distribution are the precursors to bilateral renal cortical necrosis, which is the cardinal pathological feature of the generalized Shwartzman phenomenon. It occurs in all kindneys of rabbits that develop cortical necrosis and, according to Thomas, is the "key to the generalized Shwartzman phenomenon." Other changes in the experimentally induced reaction consist of hemorrhages in the lungs, liver, spleen, and gastrointestinal tract. Zuelzer and associates,[51] have reported five cases of bilateral renal cortical necrosis in infants with severe diarrhea and dehydration. McKay and co-workers[52] have demonstrated the same lesions in certain cases of bilateral cortical necrosis in pregnant women. These two series of Zuelzer and McKay illustrate the fact that the human being is susceptible to the generalized Shwartzman reaction.

R. G., a white male infant, was admitted from the newborn nursery on the fourth day of life with a twenty-four-hour history of vomiting and fever. The disease reached its peak of severity during the second week of illness. Recovery was felt to be apparent with disappearance of symptoms and satisfactory weight gain after the third week. He returned to the hospital three days after discharge with severe vomiting and diarrhea and for the second time a near-pure culture of *E. coli 0-111 B-4* was found in his stools. Fluid balance was maintained during the next three weeks with no less than 400 to 500 c.c. per kilogram per day. Frequent checks of the blood electrolytes were required in order to guide therapy. Eighteen hours before death he began having frequent mild generalized convulsions and appeared to go into a state of shock. There was mottling and moderate cyanosis of the skin and mucous membranes. Respirations became rapid and labored but the breath sounds remained clear until immediately before death. The skin was moist, and although body tissues were wasted, there was no evidence of dehydration. Complete anuria was present in the last twenty-three hours of life. There were coincident "coffee-ground" emesis and several grossly bloody and tarry stools. A thin, serosanguineous discharge exuded continuously from the upper respiratory tract. Petechiae

appeared fourteen hours before death and some coalesced to form large purpuric lesions.

Blood sodium was 142 meq. per liter; the chloride 103 meq. per liter, and the carbon-dioxide combining power 19 meq. per liter. In spite of fluid maintenance with electrolyte-free glucose solutions, blood transfusions, control of the seizures with intravenous phenobarbital and 2.5 c.c. of adrenal cortical extract per kilogram every four hours, the patient died in a state of coma and decerebrate rigidity.

ANTIBIOTIC THERAPY

Initial antibiotic therapy during the epidemic consisted of 300,000 units of procaine penicillin per day and 50 mg. of streptomycin per kilogram per day. Experience soon proved both drugs to be without effect. This finding supports those previously mentioned references.[6, 12, 17] Most patients were administered parenteral oxytetracycline (25 mg. per kilogram per day) of the intramuscular and intravenous form, and/or intravenous chlorotetracycline (25 to 50 mg. per kilogram per day) or intramuscular polymyxin B (2.5 mg. per kilogram per day) also without benefit.

Chloramphenicol was not given a clinical trial except terminally in three cases. This strain of *E. coli 0-111 B-4* was found to be resistant to all the tetracycline drugs, penicillin, streptomycin, and polymyxin B in vitro. It was highly sensitive to chloramphenicol in dilutions of 1.0 microgram per cubic centimeter. Bacitracin and neomycin were initially not tested. Stulberg and associates[44] and Wheeler and Wainerman[45] have more recently reported success with neomycin, particularly against chloramphenicol-resistant strains of the organism. In their experience there was no emergence of neomycin-resistant strains. Subsequently, strains of the organism, perpetuated in the laboratory since the outbreak at Fort Belvoir, have been tested and found highly sensitive to neomycin. Chloramphenicol has been cited as the drug of choice, with dramatic results, in several reported epidemics associated with this organism.[6, 12, 15, 16, 18, 38] Equally successful results, however, have been reported with chlorotetracycline[12] and oxytetracycline.[17]

DISCUSSION

Bacteriological and clinical findings in this epidemic not only support the concept of an etiological role of certain strains of *E. coli* in the causation of gastroenteritis but enhance it with strong immunological evidence. Concurrent virus studies were as exhaustive as any reported with such *E. coli* outbreaks.[30]

The organism appears to be most severe in small infants with a prolonged and toxic course characterized by many exacerbations and remissions. Recovery in the face of inadequate antibiotic therapy seems to be dependent on the ability to form antibody. In the fatal case of R. G. there was no antibody titer rise evident on the second admission from the measurement taken at the onset of symptoms. Several of the survivors had antibody titers of 1:320 by the fourth week after onset.

It appears that breast-fed infants have a remarkably low susceptibility to infection by the organism. There were no current breast feeders among the entire fifty-one hospitalized pa-

tients. Antibody content and bacteriostatic properties of colostrum are under investigation at the present time.

The results also prompt serious consideration and evaluation of the use of a hyperimmune serum against the organism, especially since resistance of the organism has developed to all antibiotics with the possible exception of neomycin.

There are suggestions in the literature[5, 6, 12, 17] in reference to a variable toxicity pattern from epidemic to epidemic. Experimental work, largely by Kaufman and Dupont,[11] points to a biochemical as well as a toxic variation within some individual strains of *E. coli*. Other known enteric pathogens differ in their virulence even within the same strain. This may possibly account for the different mortality rates of epidemics.

Manifestations of this epidemic were the most severe in our experience. Brief mention has been made to a possible relationship of the marked toxicity and prolonged stress to the apparent adrenal insufficiency.

According to the principle of Selye's general adaptation syndrome, the adrenal glands become enlarged under acute stress. If the condition becomes prolonged, the adrenal cortex decreases in size and a state of complete exhaustion is reached. Hallman and Tahka[35] found in a series of infants with gastroenteritis evidence that the adrenal cortex was clearly reduced in size if the disease were active more than fourteen days. Yet, also, according to Selye,[39] one cannot assess dysfunction on the basis of adrenal size alone since even a normal-sized gland can be insufficient in its function if the requirement of the organism in hormones is not satisfied.

A physiological decrease in adrenal cortical function during the neonatal period has been well established.[41] Jaudon[40] described in 1946 a clinical entity in the newborn infant that he ascribed to transient adrenal insufficiency. This clinical impression has not been verified to date, but it has stimulated much experimental work concerning the role of neonatal adrenal hypofunction in the pathogenesis of certain disease states. Klein[41] pointed out that poor adrenal response as indicated by high eosinophil counts had been noted in chronic illness and following repeated surgery. During such conditions administration of cortisone or adrenal cortical extract appeared to produce clinical improvement. Our experience seemed to bear out Klein's finding. Before considering the use of adrenal hormone in severe and prolonged infection, it must be borne in mind that there is serious danger in this period of life of lowering the body defenses against infection. Smadel and associates[42] were able to circumvent this problem by the use of chloramphenicol along with cortisone in the treatment of enteric disease.

Although discussion of the pathological findings observed in this outbreak in relation to those of the generalized Shwartzman reaction are reserved for another paper,[48] brief mention of a possible adrenal hormone role should be made at this point. That the question of a relationship between adrenal cortical hormone therapy and the pathological picture is a valid one is supported by experimental work.

Thomas[43] has clearly shown that cortisone both prepares for and enhances the local and generalized Shwartzman reaction. On the other hand, in a different type of experiment, Marcus[47] and Good[46] have been able to prevent the Shwartzman reaction if cortisone is administered a few hours before the provocative injection is given. Our experience with adrenal cortical hormone does not clarify the issue. Cortisone alone was used in several of the survivors with apparent benefit. Adrenal cortical extract was given to four of the survivors and five of the fatal cases, again with apparent benefit. Administration in the latter group was limited to the last twenty-four hours of life in three of the cases, after the terminal syndrome had commenced. One patient who died received adrenal cortical extract during the forty-eight hours before death and another during the last three days of life. In the last two cases clinical improvement was noted prior to the onset of the terminal syndrome. From this experience we cannot conclude either that the hormonal therapy contributed to death or prevented death. The recent work of Marcus,[47] however, is thought-provoking in suggesting that the Shwartzman reaction may be a reflexion of adrenal hypofunction.

SUMMARY

1. We have presented our experiences with an epidemic of infantile diarrhea associated with *E. coli 0-111 B-4*, including a review of the literature dealing with the epidemiology, bacteriology, and clinical pattern of *E. coli* gastroenteritis.

2. Substantial evidence has been produced supporting this organism as the etiological agent in this epidemic to the exclusion of a viral or a symbiotic viral-bacterial etiology. Support for this contention has also been cited from the literature.

3. The severity of the illness is discussed at length, including apparent generalized stress reaction, extreme electrolyte imbalance, prolonged course, and high mortality rate.

4. The response to the antibiotics used in this epidemic was unsatisfactory. The variability of organism sensitivity reported in other epidemics is related.

5. There were terminal clinical findings and post-mortem changes resembling those of the generalized Shwartzman reaction.

6. The role of adrenal physiology in the pathogenesis and tissue changes of the Shwartzman reaction is reviewed briefly.

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Some Early Cases of Accidental Poisoning

A few days since, three children belonging to Sharon, playing in a meadow, pulled up the hemlock, or wild parsnip root, and eat of it, and in about five hours they all expired, and were buried in one grave the next day. This root is thought by some one of the greatest poisons in nature, and that an extract from it of three grains would be sufficient to kill any person—great care ought to be taken by parents to prevent their children going amongst it.

CONNECTICUT COURANT, August 14, 1775.

We hear from Brookline, that a melancholy Affair lately happened in the Family of Capt. Crafts of that Town: Three of his Children, one of the Age of about 6 years, going to School, gathered some Seeds out of a prickly Pod that grows upon Henbane, of which one of them eat a great Quantity, and poisoned himself to such a Degree that he died in a short Time after in great Agonies. Another was much poison'd and in great Distress, but is like to recover; the Third, and youngest, eating but a small Portion was not so much affected. This Henbane is not what generally bears that Name: it grows in the High-Way and is commonly known here by the Name of Devil's-Weed; it has a wide spreading Stalk and a broad Leaf, bears a large round prickly Pod and is of a bad Smell; when ripe the Pod opens, and the Seeds are like small Coffee.

BOSTON EVENING POST, August 25, 1766.

THICKENED FORMULAS: STANDARDIZATION OF PREPARATION AND A NEW METHOD OF ADMINISTRATION

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THICKENED feedings were first widely used for the medical management of pyloric stenosis. Today they are still used in the treatment of such cases as rumination, cardiochalasia, so-called neurotic vomiting, pylorospasm, postoperative vomiting in pyloric stenosis, and other unclassified pernicious vomiting. This paper is intended as an aid to the best use of this type of therapy when a trial with thickened formula seems indicated.

The subject of thickened feedings has been reviewed and no detailed description of the preparation of these formulas has been found in the American literature since those of McClure[1] and Sauer[2, 3, 4] in 1914 and 1918. These formulas were made with long-cooking wheat cereal (Farina). The modern precooked baby cereals have greatly simplified the preparation of thickened feedings. However, the prescription of a satisfactory formula with these cereals requires knowledge of their thickening qualities. It is felt that some standard is needed as a guide, especially for those who are only occasionally faced with this problem.

In the study here presented the thickening properties of the commonly used baby cereals have been evaluated and formulas are suggested for the preparation of an adequately thickened feeding with each cereal. A simple feeder for easier administration of thickened feedings will also be described.

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MATERIALS, METHODS, AND RESULTS

The Basic Unthickened Formula.—Any standard formula with 20 calories per ounce can be used.

The Measurement of Formula Thickness.—The spread on a ruled glass plate was measured.

The Standard Thickness.—The thickness of these formulas is less than suggested by McClure and Sauer but is quite thick, comparing favorably with the thickness of most canned strained vegetables.

Table of Thickened Formulas (Table I).—

Columns 1 and 2: Here are listed the amounts of cereal to be added to liquid formula to give the standard thickness. The differences in the cereals are emphasized in the second column, giving tablespoonfuls for six ounces of liquid formula. The differences in these amounts have real significance in terms of thickness.

Column 3: These calculations of calories per ounce of thickened formula are made on the basis of the unthickened formula having 20 calories per ounce plus the calories of the added cereal, and also take into account that adding the cereal increases the volume.

Columns 4 to 8: This is the composition of the dry cereals as given by the manufacturers.

Farina, a cereal which requires cooking, has been included at the bottom of the chart for the sake of comparison.

Directions for the Preparation of Thickened Formulas.—Because preparation in quantity is more difficult and sterilization changes the consistency, the following method is suggested.

1. Have the mother or the formula kitchen staff prepare a standard unthickened formula, sterilize, and store it in sterile bottles in the amounts which are indicated for each feeding.

2. At the time of the feeding, heat the formula in the bottle, add the precooked cereal, mix, and wait five minutes for complete thickening. The use of the wide-mouthed Hygeia bottle facilitates the addition of the cereal.

3. Feed from the bottle with a nipple with a 0.5 to 1.0 cm. hole or from the special feeder described below.

TABLE I. THICKENED FORMULAS
(See Text for Description)

	NUMBER OF TABLESPOONFULS PER OUNCE OF FORMULA	NUMBER OF TABLESPOONFULS PER SIX OUNCES OF FORMULA	APPROXIMATE NUMBER OF CALORIES PER OUNCE OF THICKENED FORMULA	PER CENT CRUDE FIBER	PER CENT CARBOHYDRATE	PER CENT FAT	PER CENT PROTEIN	PER CENT ASH
Rice								
Gerber's	1⅝	11	31	0.8	78.7	1.5	6.6	5.4
Heinz	1¼	7½	27	0.5	82.1	2.8	4.1	4.4
Pablum	1	6	26	0.3	80.9	1.0	6.0	3.8
Barley								
Gerber's	1½	9	29	1.0	75.1	0.9	11.6	4.3
Heinz	1¼	7½	28½	0.5	77.1	1.3	10.4	4.6
Pablum	1+	6½	26	0.7	76.4	1.0	10.5	4.4
Oat								
Gerber's	1¼	7½	29	1.2	68.6	3.8	15.3	4.3
Heinz	1⅛	7	28	1.5	67.0	7.1	15.0	5.1
Pablum	1⅛	7	27½	1.4	63.8	6.0	16.0	4.8
Mixed								
Gerber's (wheat, oat, corn, barley)	1⅔	10	30½	0.6	75.8	1.7	13.0	4.1
Heinz (wheat, oat, corn)	1¼	7½	29	0.7	73.7	3.1	12.6	5.2
Pablum (wheat, oat, corn, alfalfa)	1¼	7½	29	0.9	69.9	3.0	15.0	4.2
Wheat								
Farina	⅙	1	26	0.3	73.7	0.9	10.8	3.4

Special Feeder for Thickened Formula.—The basic idea of this feeder is to let air in above the food in the bottle so that a vacuum will not form and thick food will flow easily with the aid of gravity as the baby nurses.

This feeder was improvised from the standard Brecht feeder. Over the large end of the feeder is placed a soft nip-

ple with an enlarged hole (about 0.5 cm. in diameter). Over the small opening at the other end is placed a medicine dropper bulb. The thickened formula is poured into the feeder through the larger end with the small bulb in place. The nipple is then placed over the large end and the feeder is inverted into the baby's mouth. As the baby begins to suck, the small bulb is removed and the food flows with the aid of gravity (Fig. 1).

Fig. 1.—The use of the special feeder being demonstrated.

If the flow of food seems to be too rapid it is easily controlled by placing a finger lightly over the end and releasing again as needed.

DISCUSSION

It is felt that attempts to help babies with vomiting problems by thickening their formula sometimes fails because the formula is not adequately thickened. The idea is to put a sticky, clinging mass in the stomach that makes it physically difficult to be regurgitated. It has also been suggested that the peristaltic waves of the stomach can grab onto this food more easily and propel it forward.[5] Whatever the explanation of this phenomenon, the importance of real thickness is brought out by every discussion of this method, both by early reports in the literature and also by the descriptions in the modern texts. However, the latter are very brief and inadequate as an example of how to use this method.

As a food for babies there seems to be little or no advantage of the other cereals over rice. Benson and Kimball[6] came to this conclusion in a comparison of the many baby cereals. They found that rice cereal not only has the highest per cent of carbohydrate but also a higher proportion of this can be classed as "available carbohydrate." It also has the smallest amount of fat, protein, and crude fiber, and probably is the least allergenic of the cereals.

Of the three precooked rice cereals, Pablum and Heinz compared favorably and are preferred. Gerber's is less desirable because it forms a very concentrated mixture. Such mixtures are usually less well tolerated by small babies. Not only are they less digestible but they also cause excess amounts of proteins and salts to be absorbed that may upset a baby's immature system.

The reason that there is such a difference in the thickening qualities of Pablum and Heinz compared with Gerber's seems to be that the former have a flaky structure that absorbs and holds that milk in a gel-like mixture. Gerber's, on the other hand, disperses into the formula like a fine flour. If the thickened formula is boiled, the flakes of the Pablum and Heinz cereals seem to be changed somewhat to the flourlike form and the mixture becomes thinner. Gerber's does not change much with boiling.

Most babies who take adequate caloric amounts of the average formula described here (about 26 calories per ounce) will get an adequate minimum amount of fluids to which they can adjust their fluid balance. However, small babies on this regimen should always be watched for signs of dehydration and electrolyte retention.

Some babies with vomiting will not respond completely to the thickened formula described here. Then an even thicker mixture may be tried. Thick cereal which does not flow is most easily fed through a wide Hygeia nipple by pushing it down with a wooden stick or glass rod. Babies on such a formula will undoubtedly need supplementary parenteral fluids.

SUMMARY

1. A table is given with proportions for preparation of an adequately thickened formula from each of the precooked baby cereals. The chemical analysis of each cereal is also given.

2. An easy method of preparing thickened formula is outlined.

3. A special feeder is described for the feeding of thickened formula.

4. The merits of the various precooked cereals are discussed and the conclusion is made that two brands of rice cereal are preferred over the other cereals tested.

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ANOMALOUS LEFT CORONARY ARTERY ARISING FROM THE PULMONARY ARTERY

Report of a Case and Surgical Consideration

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ALTHOUGH anatomical origin of the left coronary artery from the pulmonary artery was described initially in 1911 by Abrikossoff,[1] it has only been in recent years that the clinical features of this anomaly have been recognized and authenticated sufficiently to warrant its antemortem diagnosis. This condition has been designated by some as the Bland-White-Garland syndrome in recognition of those individuals who so clearly described its clinical appearance.[2] Forty-two cases of this particular anomaly of the coronary arteries have been reported in infants.[1-33]

When the left coronary artery arises from the pulmonary artery it differs in many important features from other anomalies of the coronary vessels. Other anomalies of the coronary arteries interfere slightly, if any, with cardiac function, or with normal life span, but when the left coronary arises from the pulmonary artery, death usually ensues within the first year of life. In a few instances the anomaly has been reported in adults, generally as an incidental finding at autopsy.[20, 34] In such cases retrospective symptoms of cardiac disease are usually absent since adequate anastomoses exist with the right coronary artery. More complete reports are to be found elsewhere regarding abnormalities involving a single coronary,[35-40] multiple coronaries,[41] a right coronary or both coronaries arising from the pulmonary artery,[30, 42-44] and other less frequently encountered anomalies.[50-63]

This report is concerned with a patient whose left coronary artery originated from the pulmonary, in whom the clinical diagnosis was suspected, and an attempt was made to improve surgically the abnormal physiology produced by the lesion.

CASE REPORT

M. K., a 3-month-old white male, was admitted to the University of Kansas Medical Center because of roentgen evidence of cardiomegaly.* The baby was the result of a full-term normal delivery and had a birth weight of 8 pounds 4 ounces. The pregnancy had been complicated by hypertension and the mother had been told that she had "toxemia."

For the first month after birth the baby seemed quite normal. During the second month irritability and crying after feeding were noted. In the month prior to admission there was an increasing amount of irritability, progressive dyspnea and grunting respirations, and the formula intake declined. Because of the respiratory difficulties, a chest roentgenogram was made and cardiomegaly found.

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*Dr. Mary Boyden, Lawrence, Kansas, referred the patient.

Physical examination at the time of admission showed a pale, well-developed, and well-nourished male infant weighing 11 pounds 6 ounces. He was in obvious respiratory distress characterized by marked subcostal retraction and flaring of the alae nasi. The lungs were clear to auscultation and percussion. The heart was enlarged, but no thrills or murmurs were found. With severe crying the child became cyanotic. The liver was palpated 3 cm. below the right costal border; the spleen could not be felt.

Roentgenographic examination of the chest (Fig. 1) showed cardiomegaly predominantly of the left ventricle; bronchovascular markings in the upper and medial portions of the right lung were increased. Numerous electrocardiograms were characterized by deep Q waves and S-T segment elevations in Leads I, aVL, V_5, and V_7 (Fig. 2).

The clinical diagnosis was coronary insufficiency either from an anomalous left coronary artery or subendocardial fibroelastosis, with the possibility that both were present. Because of the very poor prognosis in either of these diseases when marked symptoms occur at an early age, surgical intervention was undertaken with the hope that an anomalous coronary would be found, and that improvement might be secured by constricting the pulmonary artery distal to the origin of the anomalous left coronary artery, thereby increasing blood flow through the latter.

The baby was digitalized and kept in an oxygen tent, because of the respiratory distress. On the ninth hospital day the infant was anesthetized with cyclopropane-oxygen and an endotracheal tube inserted. An inframammary intercostal incision was made through the fourth interspace. Just after the pectoral muscles had been transected, no carotid pulse could be felt by the anesthetist. Simultaneously there appeared in the electrocardiogram numerous aberrant ventricular beats with marked atrioventricular dissociation. The pleural and pericardial cavities were immediately entered and cardiac massage instituted. Despite these efforts, ventricular fibrillation occurred, and the infant died.

Pathology.—The significant findings were limited to the heart. There were no other abnormalities. The heart weighed 80 grams (average weight at this age, 23 grams). There was marked enlargement of the left ventricle with prominent aneurysmal dilatation near the apex. In this region the ventricular wall was thinned, gray, and fibrotic. In the left atrium and

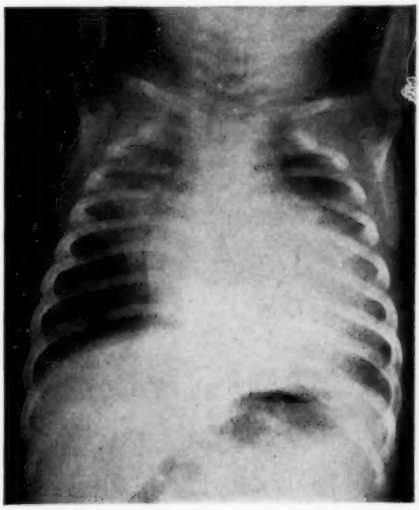

Fig. 1.—Chest roentgenogram showing marked cardiomegaly and increased bronchovascular markings, particularly on the right side.

throughout the left ventricle, but particularly at its base, there was much fibrous thickening in the endocardial and subendocardial areas. This caused a glistening appearance of the endocardium. To a lesser degree this change was noted on the left ventricular side of the interventricular septum. The chordae tendineae were thickened and trabeculated.

The heart valves appeared normal in structure, position, and size. The right coronary artery originated from its usual location in the sinus of the

right aortic cusp. However, the left coronary arose abnormally from the sinus of the left pulmonic cusp. The peripheral courses of both coronaries followed the usual pattern (Fig. 3).

On microscopic examination, sections through the left ventricle showed marked and extensive fibrous thickening of the endocardium almost replacing the myocardium at the base and

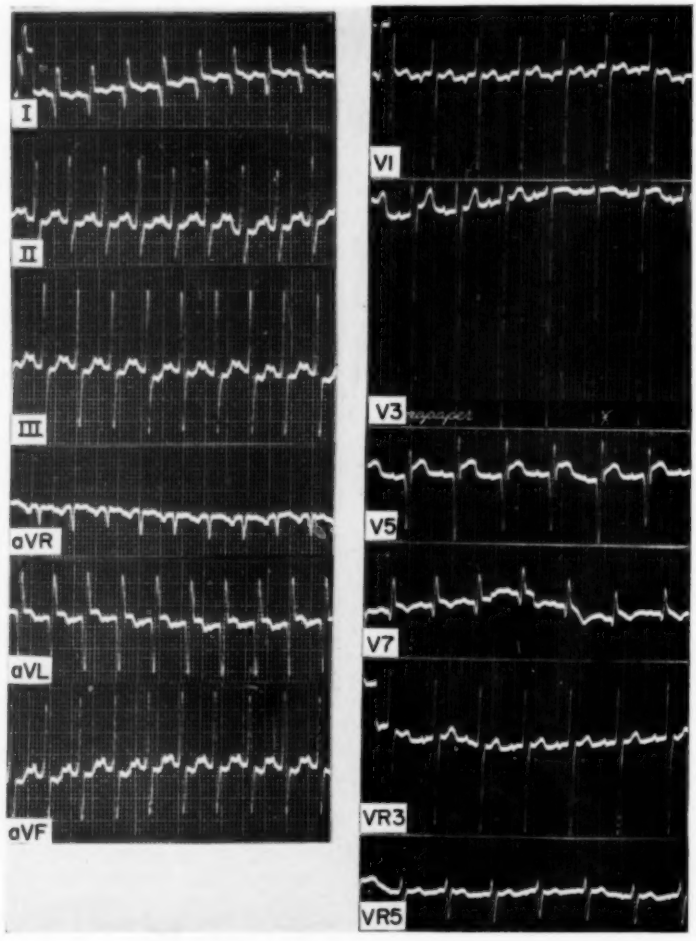

Fig. 2.—Standard and unipolar leads of electrocardiogram taken several days after admission. Note deep Q waves and S-T segment elevations in Leads I, aVL, V_5, and V_7, along with T-wave inversion in I and V_7.

Prior to fixation, radiopaque material injected into the ostium of the left coronary demonstrated numerous anastomoses between the left and right coronary arteries (Fig. 4).

apex. Numerous fat droplets were noted in the myocardium of the left ventricle. Intermingled in the regions of fibrosis were punctate areas of calcification, these being found particu-

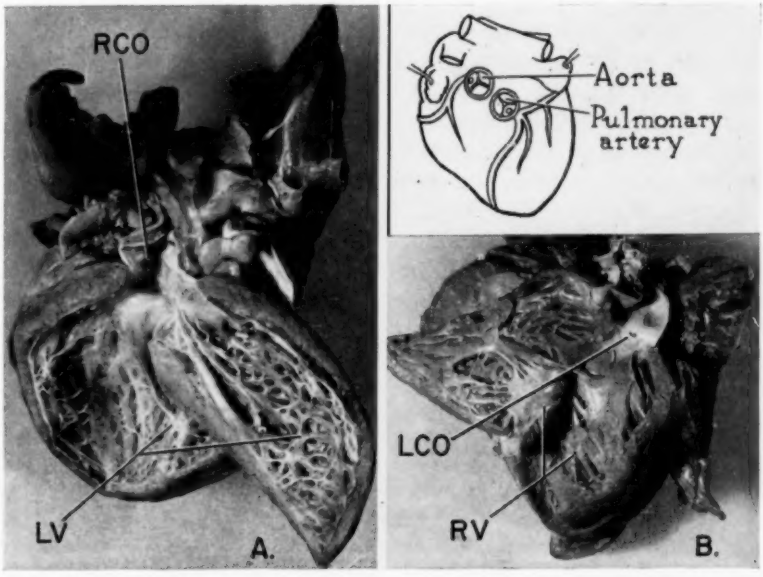

Fig. 3.—Photographs of opened specimen showing interior of left ventricle and aorta, *A*; right ventricle and pulmonary artery, *B*. *RCO*, Ostium of right coronary artery; *LV*, left ventricle; *LCO*, ostium of left coronary; *RV*, right ventricle.

larly in the papillary muscles. No appreciable fibrosis was seen in the right ventricle.

DIAGNOSIS

Although the occurrence of anomalous origin of the left coronary artery from the pulmonary artery is relatively infrequent, the physician caring for children will probably encounter at least one such case during his years of practice. The astute practitioner should consider the possibility of coronary insufficiency in the differential diagnosis of young infants who, although appearing normal at birth, become fussy and irritable at several months of age, especially after feedings. The presence of an angina-like syndrome in an otherwise healthy infant without cyanosis or cardiac murmurs should suggest the possibility of a left coronary artery arising from the

Fig. 4.—Roentgenogram of gross specimen after injection of Diodrast into anomalous left coronary artery. Numerous anastomoses are demonstrated as well as good filling of the right coronary artery.

pulmonary artery. This syndrome manifests itself by episodes, usually postprandially, of screaming and drawing up of the legs, followed by tachypnea, profuse diaphoresis, pallor, and occasionally cyanosis. The suspected clinical diagnosis usually can be confirmed by electrocardiographic and roentgen studies. Fluoroscopy demonstrates significant cardiac enlargement, particularly of the left ventricle. Pulsations of the heart are weak or diminished and occasionally an aneurysm of the myocardium can be visualized. The lung fields do not appear unusual unless pneumonia or pulmonary edema is present.

The electrocardiogram, when associated with the clinical history of the infant, may be pathognomonic of anomalous origin of the left coronary artery from the pulmonary artery. The pattern is that of myocardial ischemia and injury not unlike that encountered in older individuals with occlusion of the anterior descending branch of the left coronary artery. Other conditions causing left ventricular hypertrophy and/or ischemia may be confused, but the appearance of deep Q waves in the leads over the left ventricle with significant T-wave changes will distinguish the anomalous coronary artery.

Subendocardial fibroelastosis is not infrequently associated with anomalous origin of the left coronary artery from the pulmonary artery. Indeed, most of the reported instances of the latter have described this combination. In subendocardial fibroelastosis alone the electrocardiogram usually shows subendocardial ischemia and/or left ventricular hypertrophy rather than a classical infarction pattern. However, electrocardiograms in fibroelastosis vary considerably and do not have a consistent appearance.

Other lesions causing acyanotic cardiomegaly in infancy usually have a significant murmur and should be excluded by clinical observation, angiography, or physiologic studies such as cardiac catheterization. It may not be possible to exclude from the differential diagnosis such rare cardiopathies as glycogen storage disease or rhabdomyoma of the heart.

DISCUSSION

Pressure relations in the greater and lesser circulations of the fetus cause blood to flow from the pulmonary artery to the aorta via the ductus arteriosus. Perfusion pressure in a left coronary artery arising from the pulmonary artery in the fetus is greater than in the left coronary artery arising normally from the aorta. Therefore, flow in the anomalous left coronary artery should be adequate in the fetus. Subsequent to birth, however, the pulmonary artery pressure gradually decreases relative to the aortic pressure increase and consequently flow through the left coronary artery becomes less.[64]

Myocardial oxygenation is dependent primarily on coronary flow, the oxygen content being sufficient if the blood is more than 60 to 80 per cent saturated. The main factors affecting coronary flow are vessel diameter and perfusion pressure. When the latter falls to a level not permitting adequate flow, myocardial ischemia ensues. Under such circumstances anastomotic channels between coronary arteries dilate. The direction of flow may reverse in the anomalous left coronary artery when it originates from the

pulmonary so that blood from the right coronary artery actually flows in a retrograde direction to the pulmonary artery.[65] In the few patients who have survived to adult life with this anomaly, these collateral channels are undoubtedly well developed.

Following birth, the work load placed on the left ventricle gradually increases not only because of a different circulation from that in fetal life, but also because of the demands of growth. This is reflected normally by a comparatively enlarging left ventricle. The rising oxygen demands of the left ventricle usually cannot be met by the falling perfusion pressure in the anomalous left coronary despite anastomotic channels with the right coronary system. In addition, the fibrosis in the subendocardial areas may impede coronary flow by preventing relaxation of the myocardium during diastole. Aneurysmal formation secondary to ischemic or fibrotic areas further decreases left ventricular output. These concepts explain the asymptomatic period seen in this condition immediately following birth and the occurrence of symptoms several months after birth.

Adequate blood flow through a left coronary artery originating from the pulmonary artery must be established if these infants are to survive. The outlook for life is usually poor since anastomotic circulation alone is seldom adequate. As pressure is the most important factor in determining flow, some means of elevating the pressure would be desirable. Gasul and Loeffler[15] were first to suggest an aortic-pulmonic artery communication as a means of increasing pulmonary artery pressure as well as oxygen content of the left coronary blood. Potts[66] has used this procedure in two patients without success. This technique has the serious disadvantage of increasing the work load of an already damaged left ventricle, a criticism probably exceeding any benefit which might be obtained by increasing the pulmonary artery oxygen saturation.

Another method under consideration is excision of that part of the pulmonary artery containing the left ostium and transplanting it to the aorta while perfusion is being maintained artificially with a syringe and vessel catheter. This procedure, if successful, would give the ideal anatomic and physiologic result; unfortunately, its technical difficulties are many. In at least one clinic this is the proposed procedure of choice when an anomalous left coronary arising from the pulmonary is encountered.[67] Hypothermia or cross-circulation may make such an operation more feasible.

Other methods of increasing or establishing circulation to the myocardium such as pericardial tale insufflation, omentopexy, and other related procedures would not offer enough additional circulation immediately to warrant their use, although experimental studies of a jejunal flap appear encouraging.[68]

Creating pulmonary artery hypertension may be the most practical and satisfactory method of increasing the effective coronary flow. It had previously been demonstrated in our laboratory that sustained pulmonary hypertension could be produced by deliberate constriction of the pulmonary artery, a procedure previously described elsewhere.[69] This operation is technically simple and has the advantage of increasing the work load of the right ventricle only, an important

consideration since that portion of the heart is essentially normal in this syndrome. It is believed that the stenosis so established would be sufficient to enable the infant to survive, and perhaps develop more collateral circulation, without being severe enough to cause the difficulties encountered in congenital pulmonic stenosis.

The severity and extent of the gross and microscopic changes in the heart in an anomalous origin of the left coronary artery raise the question as to their reversibility. However, since the infant with this congenital malformation almost invariably has an unfavorable outcome, surgical intervention as a palliative or possible curative treatment must be considered.

SUMMARY

1. The report of a 3-month-old male infant with a left coronary artery arising from the pulmonary artery is presented. The symptomatology and clinical and laboratory findings are given. Operation was attempted to increase blood flow through the anomalous artery.

2. The physiology of this type of coronary artery anomaly is briefly discussed. Attention is directed to several operative procedures that might be used in reinstating an adequate blood supply to the heart.

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CONGENITAL VALVULAR OBSTRUCTION OF THE POSTERIOR URETHRA IN TWO BROTHERS

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ALTHOUGH many cases of congenital vesical neck obstructions in children have been described in the literature, its occurrence in siblings has rarely been reported. A review of the literature reveals only one report in which Rolnick[1] briefly mentions the presence of valves in newborn twins in his textbook. The increasing frequency with which valves are being described has been dependent on the development of better infant cystoscopes and an increasing cognizance on the part of physicians that persistent urinary symptoms in children warrant urological investigation.

The first case of this type recognized in the United States by autopsy, according to a report from the medical and pathological department of Johns Hopkins Hospital, was that of Knox and Sprunt[2] in 1912. Autopsy finding showed an obstruction of the posterior urethra by a ridge immediately below the verumontanum, which divided into two prominent diverging folds in the posterior wall of the urethra. Hugh Young in 1912 is credited with having diagnosed and successfully removed the obstruction caused by posterior urethral valves. Another early report was made by Lowsley[3] in 1914 on an autopsy upon an infant 3 months old who showed valvular obstruction at the lower end of the verumontanum, in addition to bilateral hydronephrosis, and hydroureters.

In 1919 Young and associates[4] reported twelve cases, in none of whom had the clinical diagnosis been made or operation carried out; consequently the true condition was not recognized until autopsy. After this report, however, numerous clinical cases were reported and in 1929 Young and McKay[5] gave an excellent monograph of the subject.

Recently, in this institution we had the presence of posterior urethral valves in brothers which led us to look into a question of the lesion being due to a hereditary trait.

It is sometimes presumed that if a disease occurs in both of identical twins this proves the hereditary nature of the disease. Actually this inference, if not admissible for environment of such a pair of twins, must be much more similar than two ordinary brothers or sisters. The presence of a disease in both of a pair of identical twins, however, taken together with instances of the same disease occurring in only one of the fraternal twin pairs, can be generally used as an argument in favor of hereditary influence of the disease in question. One of the most important consequences of the acceptance of Mendel's laws is that the results of the study of heredity can

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be expressed numerically in exact arithmetical proportion in the offspring of different geno types.[6] One urological condition which can be expressed numerically and is therefore hereditary is renal polycystic disease.

A disease can occur by mere chance in more than one member of the same family and this apparently is the situation found in the following case reports.

CASE REPORTS

CASE 1.—V. P. III (No. 225274), a 7-month-old Negro male, was brought into the outpatient pediatric clinic on Sept. 10, 1953, by his mother who gave a history that the child had had fever and a swollen abdomen which had developed in the preceding twenty-four hours, causing the child to be very fretful.

The patient's mother was 21 years of age and was well. The 26-year-old father was estranged from the mother but when last seen was in good health. There was a history that four of the father's brothers died in infancy but the cause was not known and could not be traced.

The past history revealed that the child was delivered at term after a normal labor. He was the third born, having an older brother 22 months old and a sister 4 years old. He had apparently been developing normally until the onset of the present illness.

Physical examination on admission revealed a well-developed and well-nourished Negro boy who was lethargic and fretful during the examination. The temperature was 104.4° F., the pulse 160 per minute, the respiration 72 per minute, and the weight was 16 pounds 10 ounces. The blood pressure on admission was 150 systolic and 90 diastolic and ranged between 150/90 down to 140/80 during the entire hospital stay. The abdomen was moderately distended, tympanitic with a tender firm mass in the left upper quadrant measuring 10 by 12 cm., and a similar mass in the right upper quadrant measuring 5 by 6 cm. No peristaltic waves were heard on auscultation.

The blood on admission demonstrated a hemoglobin of 10 grams and a leukocyte count of 10,000 per cubic millimeter with 68 per cent segmented polymorphonuclears, 4 per cent band forms, and 28 per cent lymphocytes. A sickle-cell preparation was negative. A voided urine specimen was chemically negative and showed a few clumps of leukocytes on centrifuged microscopic examination. A urine culture obtained on admission revealed a member of the coli-aerogenes group. On admission the nonprotein nitrogen was 43 mg. per 100 c.c., carbon dioxide combining power 14 meq. per liter, potassium 7.0 meq. per liter, and chlorides 116/meq. per liter. A stool culture was negative for enteric pathogens.

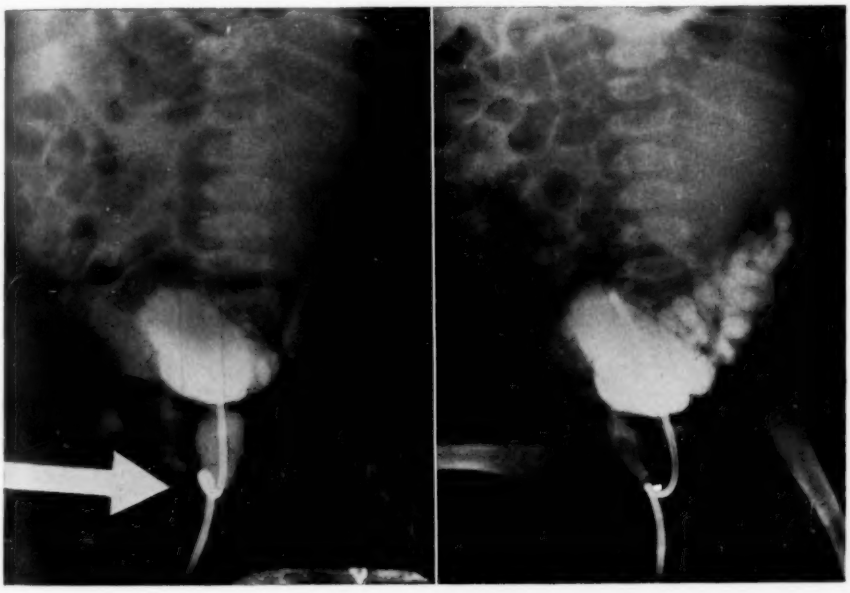
Roentgenographic examinations of the chest and long bones were normal and a film of the abdomen revealed bilateral flank masses.

In view of the critical condition of the patient, a surgical consultation was obtained and the impression of an acute peritonitis secondary to a perforated viscus was entertained, but because of the poor status of the patient, conservative therapy was advised and carried out, using penicillin, streptomycin, and Terramycin in heroic doses. A urological consultation was obtained, at which time a catheter was inserted into the bladder and 50 c.c. of residual urine was obtained. Two excretory urograms were unsatisfactory due to poor excretion of the media. A delayed fluid cystogram using 5 per cent sodium iodide solution revealed the obstructive factor and ureteral reflux on the left (Fig. 1). A small Foley catheter was then left in the bladder and vigorous therapy in correcting electrolytes and fluid balance was continued. The patient became afebrile for five days on catheter drainage, but on the ninth hospital day the catheter became occluded for several hours, after which, despite large doses of

Chloromycetin, Terramycin, and streptomycin, he continued a febrile course with increasing renal failure until he died on the fourteenth hospital day. Just before death the nonprotein nitrogen was 89 mg. per 100 c.c., carbon dioxide combining power was 14 meq. per liter, and the chlorides were 97 meq. per liter.

Necropsy was performed six hours after death. Pertinent gross and microscopic findings were as follows: The organs of the urinary system showed large. The renal calyces were greatly dilated and contained large amounts of green mucoid material. The pelvis on this side was tremendously dilated and measured 5.6 cm. from the kidney substance to the outermost portion of its circumference. The entire anatomical arrangement of the organ was severely distorted, the pyramids being entirely obliterated.

The ureters were very tortuous, long, widely dilated, and both became larger in the distal portion and at one point



A. *B.*

Fig. 1.—*A*, Fluid cystogram of patient in Case 1, showing trabeculated bladder and dilated posterior urethra. *B*, Delayed cystogram showing ureteral reflux and mass in left flank.

the right kidney to have fetal lobulations and was larger than the left, measuring 11 by 7 by 3½ cm. The pelvis of the kidney was so dilated that it considerably exceeded the parenchyma in size. The left kidney showed more pronounced fetal markings. The organ was 10 cm. in length, 5.5 cm. in width, and 5 cm. thick. On the anterior and outer surfaces of the lower half of the kidney, there were numerous retention cysts which were quite reached a circumference of 3.0 cm. (Fig. 2).

The bladder was markedly enlarged and thickened. The ureteral orifices were increased in size but were in the usual position.

A number of prostatic duct openings were observed in the dilated posterior urethra. At its widest portion the verumontanum measured 5 by 4 mm. At its lowermost portion, a particularly interesting arrangement was no-

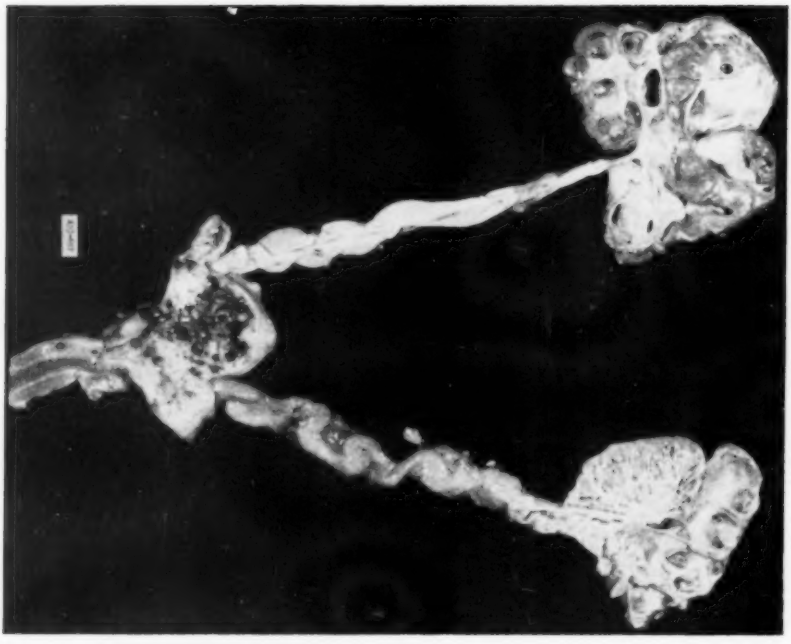


Fig. 2.—Autopsy specimen of the entire urinary tract. Note the dilated and tortuous ureters and the marked hydronephrosis.

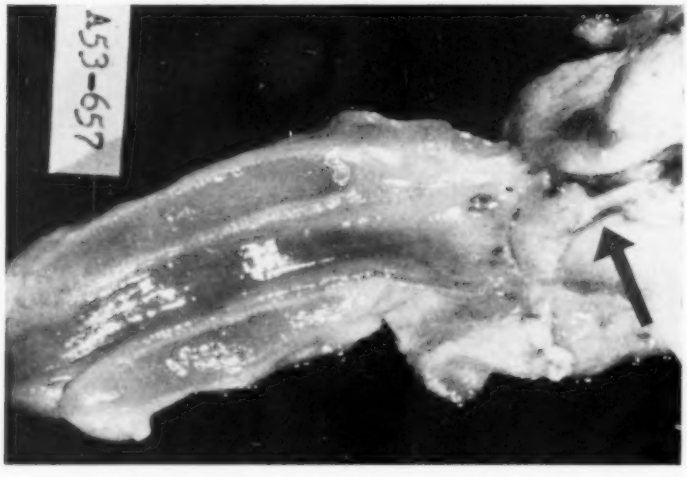
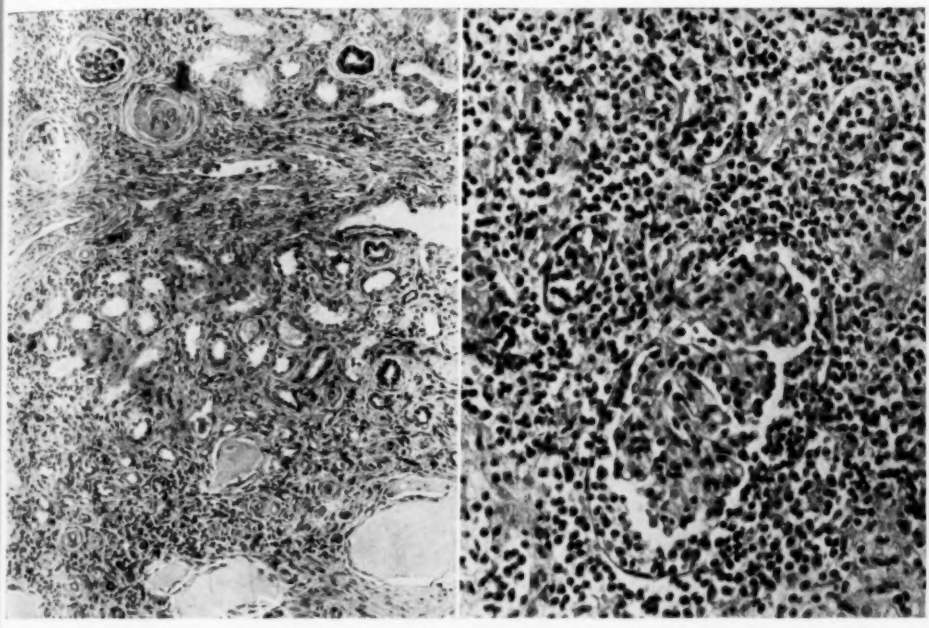


Fig. 3.—Autopsy specimen of the urethra; arrow points to the urethral valve.



A. *B.*

Fig. 4.—*A*, Kidney showing hyalinized glomeruli, atrophic tubules, and increased interstitial fibrosis, consistant with chronic pyelonephritis. *B*, High-power view of glomerulus with thickened Bowman's capsule.

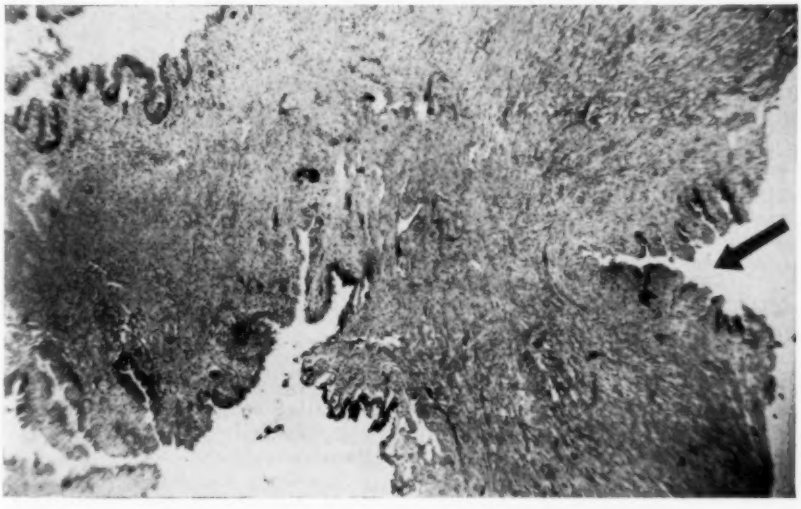


Fig. 5.—Arrow points to the slitlike lumen of the urethra in the region of the valve.

tieed. A ridge continuous below the verumontanum divided into two prominent forklike processes which attached themselves closely to the entire urethral circumference instead of folding out gradually on the posterior wall of the membranous urethra (Fig. 3). The mucosa of the dilated prostatic urethra and the anterior urethra was markedly congested and resembled that of the bladder in appearance.

The microscopic sections of the kidneys revealed a typical picture of compression due to hydronephrosis. Numerous polymorphonuclear neutrophils were found throughout the renal interstitial tissue, some in massive accumulations. The renal tubules were undergoing necrosis and were atrophic. The glomeruli were widely separated and greatly reduced in number and Bowman's capsule was thick and fibrosed. The interstitial connective tissue was increased and the picture was that of chronic pyelonephritis (Fig. 4*A* and *B*).

Microscopic sections of the verumontanum were interesting, in that, by the use of van Gieson's stain, it was observed that while there was a sprinkling of muscular elements throughout, the lower portion was made up mostly of connective tissue fibers. Cross section at the point of obstruction showed a very small slitlike lumen lined with stratified epithelium, resting on a feltlike base under which there was a very thick mucosa (Fig. 5). Surrounding this there was an extensive area rather densely arranged, made up of connective tissue and smooth muscle fibers. The section of prostate showed hyperplastic figures. The final pathological diagnosis was valvular obstruction of the urethra at the bulbomembranous junction (type 1).

CASE 2.—L. L. P. (No. 193545), aged 22 months, was referred to the pediatric clinic on Oct. 1, 1953, after his younger brother had died one week earlier with posterior urethral valves as the etiological factor. Questioning of the mother revealed that the patient had had frequency and a narrow stream all his life. The child was delivered at term, and other than several episodes of diarrhea and diaper rash, the child had been in good health since then.

Physical examination revealed a well-developed, well-nourished, chubby, Negro boy who appeared quite healthy. The temperature was 100.4° F. rectally, the pulse was 100 per minute, respirations 30 per minute, and the blood pressure varied from 84/50 to 115/60. The patient weighed 22 pounds. The remainder of the physical examination was not remarkable. Cystoscopy, performed under drop ether anesthesia, revealed a type 3 or "iris" type of valvular deformity proximal to the verumontanum. The bladder was markedly trabeculated and the residual urine determination was less than 5 c.c. A fluid cystogram revealed a small bladder without demonstrable reflux, although the posterior urethra was dilated, very similar to that seen in the case of his brother (Fig. 6 *A*). Excretory urography revealed slight dilatation of the pelves, calyces, and ureters bilaterally (Fig. 6 *B*). Urinalysis revealed a grade IV puria, and a culture of the urine revealed coli-aerogenes and *Pseudomonas aeroginosa*. The hemoglobin on admission was 11 grams and the leukocyte count was 15,150 cu. mm. with an essentially normal differential count. Blood nonprotein nitrogen was 31 mg. per 100 c.c., creatinine 0.8 mg. per 100 c.c., carbon dioxide combining power 16 meq. per liter, and chlorides 89 meq. per liter.

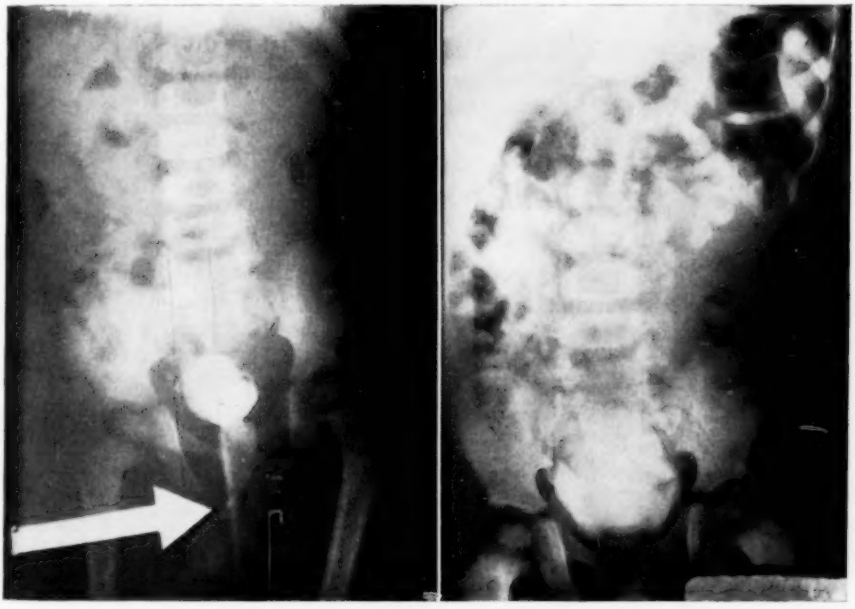
On the fifteenth hospital day a retropubic exploration of the posterior urethra was done and the iris-type valve was excised. A No. 16 French Foley catheter was brought out the dome of the bladder and a No. 12 French Foley catheter was left in the urethra as a splint. The postoperative course was stormy, requiring a repositioning of the suprapubic tube, but on the seventy-eighth hospital day, the patient was discharged from the hospital with a nonprotein nitrogen of 38 mg. per cent. Subsequent visits to the outpatient clinic revealed that the

child was growing normally and that the upper urinary tract was functioning well, as demonstrated by excretory urography six months after his discharge from the hospital.

On June 2, 1954, a transurethral resection of the contracted vesical neck was done and a tag of the urethral valve was excised, using the No. 16 French Braasch-Bumpus punch. The patient still wears the suprapubic tube as an emergency outlet.

the posterior portion of the verumontanum to the vesical outlet (type 2). The diaphram or "iris" (type 3) may be seen in varying positions in relationship to the verumontanum, which in itself is generally anonymous, being either elongated, enlarged, or misplaced.

The embryological etiology of posterior urethral valves is uncertain.



A. *B.*

Fig. 6.—*A*, Fluid cystogram of patient in Case 2, showing a dilated posterior urethra, similar to that seen in his brother. *B*, Excretory urogram on patient in Case 2, preoperative.

COMMENT

Valves of posterior urethra have been classified into three types by Young, depending upon their relationship to the verumontanum to which most valves are attached at some point. The most common type extends from the anterior end of the lateral wall (type 1), but they may extend from

Tolmatschew, Lindeman, and Welchens believe that they are simply overgrowth or hypertrophy of normal folds. Bazy[7] proposed that the persistance of the urogenital membrane was the etiology, while Lowsley[3] advanced the theory of anomalous wolffian and müllerian duct developments. Watson[8] in 1918 was able to demon-

strate in sections of the verumontanum of a 14-week-old fetus fibrous strands connecting the tip of the verumontanum with the roof of the urethra.

The diagnosis is confirmed by fluid cystography with refluxing ureters many times when excretory urography reveals only poor or delayed renal function. Urethrocystoscopy performed by a direct vision instrument confirms the diagnosis when the valves are seen.

The pathological changes found on urological investigation are those commonly seen with infravesical obstructions. The valvular effect of the membranes produces a ballooning out of the cusps with the concave surface always toward the bladder. Fluids injected urethrally, therefore, are almost never obstructed from flowing into the bladder. The posterior urethra proximal to the valves almost always becomes dilated and continuous with the bladder, a fact that can be usually demonstrated along with the cresentic appearance of the valves, if after a radiopaque fluid is injected into the bladder, the patient is placed in an upright position for the exposure. The detrusor becomes hypertrophied, cellules appear in the bladder, and in almost every case, the ureteral orifices are patulous. Early, the bladder capacity usually varies inversely with the degree of hydroureter and hydronephrosis. Distention of the bladder from valvular obstruction usually comes late with only approximately 20 per cent of children in a large series of cases reported carrying over 4 oz. of residual urine in the bladder.[9] The ureters become markedly elongated, kinked, and distended, even to the size of the colon, with the left renal unit most often the one more greatly involved. With the intervention of infection, this process is accelerated, causing the thin-shelled renal parenchyma to undergo even further atrophy. Progressive renal damage, as demonstrated by phenolsulfathalein excretion tests, progresses until the obstructive factor or factors are removed. Patients with marked valvular obstruction rarely live longer than 10 years, although we have recently seen a 23-year-old patient who died of renal insufficiency from this condition.

Hypertension as occurred in one of our cases occurs only with marked glomerular damage, but is rarely found in valvular obstruction where the damage is chiefly tubular.

Symptoms of valves of the posterior urethra are those of obstruction plus renal insufficiency, uremia, and usually infection. The symptoms when carefully obtained, date back to birth and are urinary frequency, dribbling, and dysuria, which unfortunately is most often mistaken for enuresis, until the child is 3 or 4 years old. Unless infection intervenes, most of these patients have marked irreversible changes before they are first seen. Even when the diagnosis is made at time of birth in many cases, the damage is severe as renal function begins with the fifth month in utero and the damage is further evidence that the fetus voids during the later period of his intrauterine life.

Treatment of these patients may be by either transurethral resection of the valves as indicated by Young, Campbell, and others or the retropubic approach as advocated by Millen and Burns. The perineal approach as suggested by Young in 1919 is a third operation available. Surgery should be delayed long enough to allow renal

function to improve and any acute infection to subside. The generous use of antibiotics and chemotherapy both before and after surgery is advised, along with vigorous regulation of the electrolytes and fluid balance.

Prognosis depends upon the degree of permanent renal insufficiency but many of these patients, if relieved of the obstruction and are maintained with a sterile urine, can live healthy and productive lives. Unfortunately the majority when first seen have advanced renal damage which makes the prognosis guarded, to say the least.

As indicated by these case reports, congenital deformities in the urinary tract may occur in siblings, as demonstrated recently by Lattimer[10] in identical twin boys with glandular hypospadius and meatal stricture. When a child with congenital malformation is found, questioning of the parents concerning the other children should always be done, and if any urological symptoms are present, excretory urography should be performed, followed by other urological investigation if necessary. Only by such investigation as this was our second case found early.

SUMMARY

A case report of two brothers is presented, both of whom had posterior urethral valvular obstruction. The younger brother's condition was confirmed by necropsy and the older sibling, whose case was discovered through direct inquiry of the mother, was determined at cystoscopy and then corrected surgically. A review of the historical background of urethral valves is given followed by a brief discussion concerning the diagnosis and management of this condition. When a young patient with a urological anomaly is found, the parents should always be questioned concerning the siblings.

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A METHOD FOR THE MAINTENANCE OF NORMAL BODY TEMPERATURE DURING BLOOD EXCHANGE IN THE NEWBORN INFANT

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WHILE the exchange of blood in the erythroblastotic infant constitutes a safe and lifesaving procedure, it must, nevertheless, be looked upon as one involving no small degree of stress. Among other measures for minimizing such stress, the maintenance of a normal body temperature during the exchange appears highly desirable from the most fundamental physiologic standpoint.

Having been repeatedly disappointed with the efficiency of improvised measures to this end, including the use of hot-water bottles and the prewarming of the flask of donor blood, a study of more reliable methods was undertaken, resulting in the design, test, and routine use of the apparatus described.

The equipment consists of an electrically heated exchange table in the form of a thermostatically controlled water bath, together with a constant temperature water-jacket for the blood flask. Both are maintained at 37° C. Table and flask holder are of stainless steel. The use of the apparatus has been found so eminently satisfactory that it was thought desirable to make the details of its design available to others. The table, with its oxygen and humidifying tent of plastic material, readily accommodates infants of varying sizes and requires little storage space in the treatment room. The table has been used in performing approximately nine exchange procedures to date without perceptible change in the patients' temperature and with most satisfactory results in each instance.

Fig. 1 shows the details of the design. Dimensions were established through measurement of infants in the nursery and further checked by means of a preliminary wooden "mock-up." Cost of the electrical equipment totaled less than sixty dollars, the metal work being done by tinsmiths in the hospital shops. Fig. 2 shows the equipment in use.

While the design has proved highly satisfactory in the hands of our pediatric staff, many improvements will doubtless suggest themselves. For example, a means for the rapid emptying of the water-jacket would be very desirable. At present, however, members of the house staff have expressed reluctance to dispense with the table while this modification might be made, since need for its immediate use might arise.

ADDENDUM

Since this paper was written, this apparatus has been found most valuable in handling shock problems of any nature.

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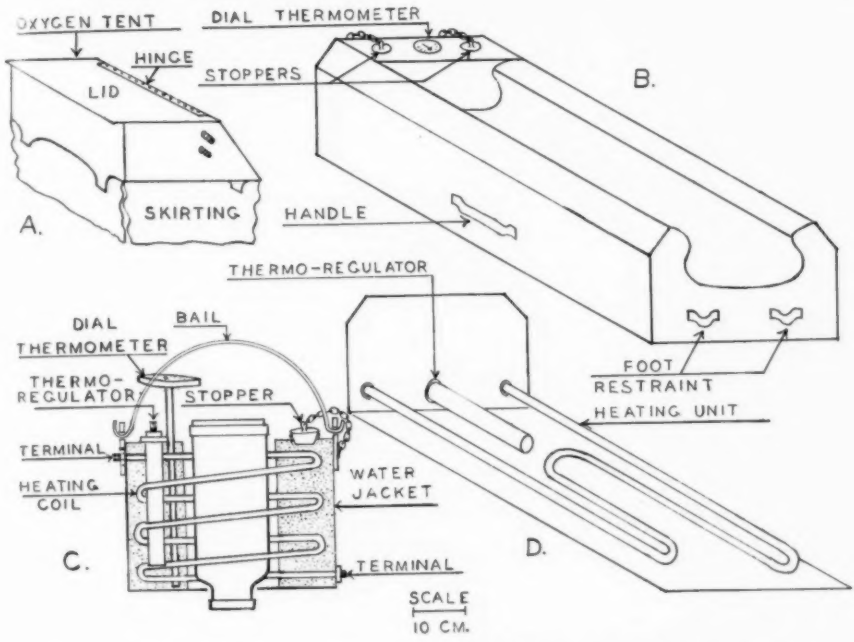

Fig. 1.—Details of the Virginia exchange table, blood-warming unit, and oxygen tent.

Fig. 2.—The Virginia exchange table in use.

CARBONIC ACID GAS AS A CONTRAST MEDIUM IN THE RADIOGRAPHY OF INFANTS AND CHILDREN

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NEW HYDE PARK, L. I., N. Y.

AMONG the desirable attributes of radiographic contrast media are that they be readily available, inexpensive, and easily administered. The average child is willing to concede these advantages to a bottle of any familiar carbonated soft beverage. During the past years we have frequently employed this method of introducing gas into the stomach for contrast purposes, and have found it a useful aid to radiologic examination.

The average carbonated beverage contains 3.5 c.c. of carbon dioxide gas with each cubic centimeter of liquid under standard conditions. By administering 100 c.c., approximately 350 c.c. of carbonic acid gas is liberated within the stomach. At body temperature a somewhat greater volume of gas is made available. It is advantageous to let the patient take the drink at room temperature rather than chilled. One of the manufacturers of a popular soft drink suggested that the patient be permitted to drink directly from the bottle inasmuch as some of the carbon dioxide was lost while the drink was poured into a glass. The surface conditions of the receptacle as well as contact with the atmosphere may favor rapid liberation of gas.[1]

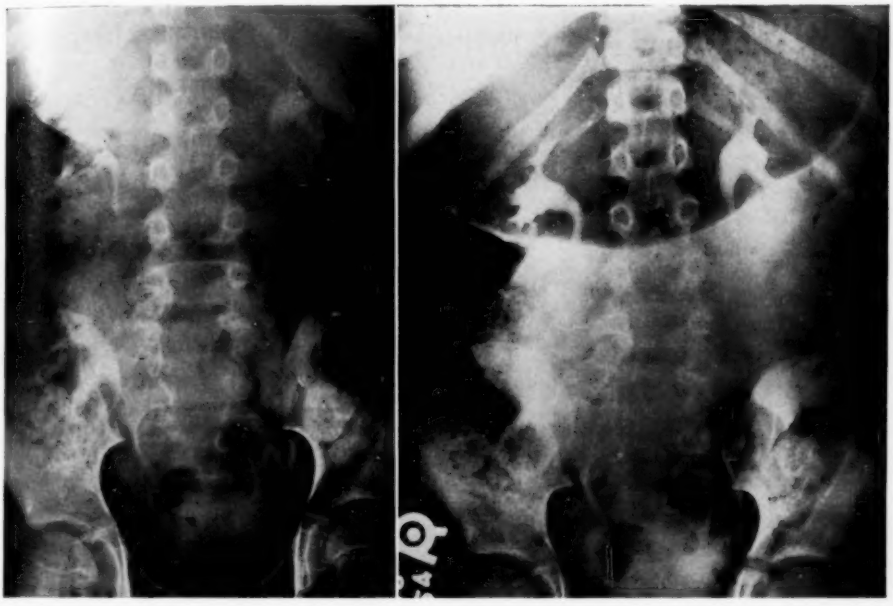
There are two fields of usefulness for carbonated drinks in pediatric radiology. The first is distention of the stomach with gas as an aid to visualizing the kidneys. The control film is taken, and before going on with the urography, the bottle of soda is prominently displayed to the child as a reward for good behavior. The average youngster of from 2 to 10 years of age seems to welcome the idea that something pleasant will follow the painful experience. The patient is permitted to drink his bottle just before the succeeding films are exposed. We have noted no impairment of kidney visualization after the administration of the fluid. The renal pelves and calyces are brought into sharp relief by the elimination of overlying gas shadows, which are displaced by the distended stomach (Figs. 1 and 2).

In the radiography of infants, the carbonated beverage may be given

From the Department of Radiology, The Long Island Jewish Hospital.

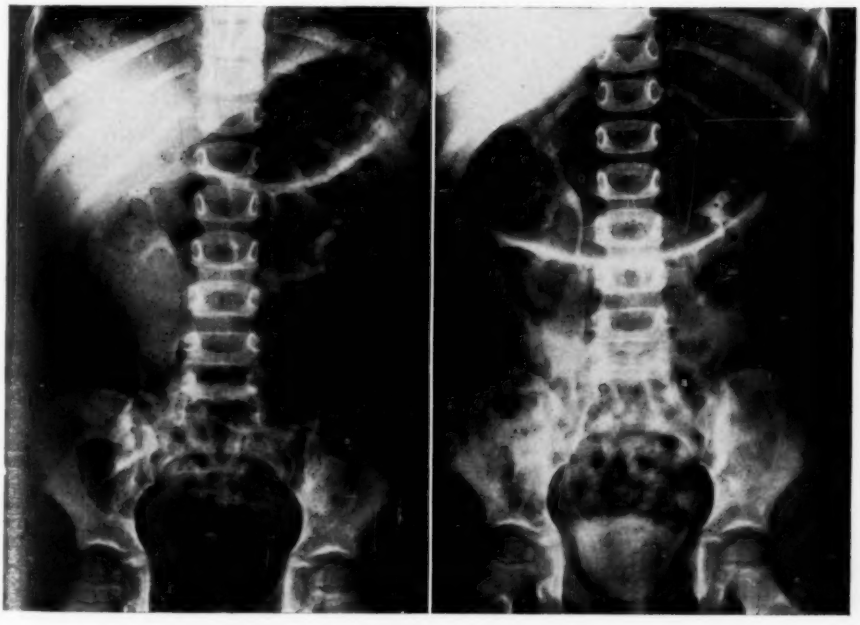
Fig. 1.—*A*, Intravenous urogram four minutes after injection of 15 c.c. of Diodrast compound solution in a 10-year-old boy who had been operated upon in infancy for a myelomeningocele in the lumbosacral region. The renal pelves and calyces are obscured by overlying gas and fecal shadows. *B*, Same patient as *A*, ten minutes after Diodrast. The patient had been given 150 c.c. of a carbonated beverage three minutes before this film was taken. The stomach is distended with carbonic acid gas, and the kidney pelves and calyces are seen to better advantage than on the previous film.

Fig. 2.—*A*, Intravenous urogram made five minutes after the injection of 15 c.c. of Hypaque in a 4-year-old child. The kidney pelves are obscured by overlying gas shadows. *B*, Same patient as *A*, ten minutes after injection and three minutes after drinking 100 c.c. of a carbonated beverage at room temperature. The dilated stomach permits better visualization of the renal pelves and calyces. A double kidney pelvis is seen on the left side.



A. *B.*

Fig. 1.—(*For legend, see opposite page.*)

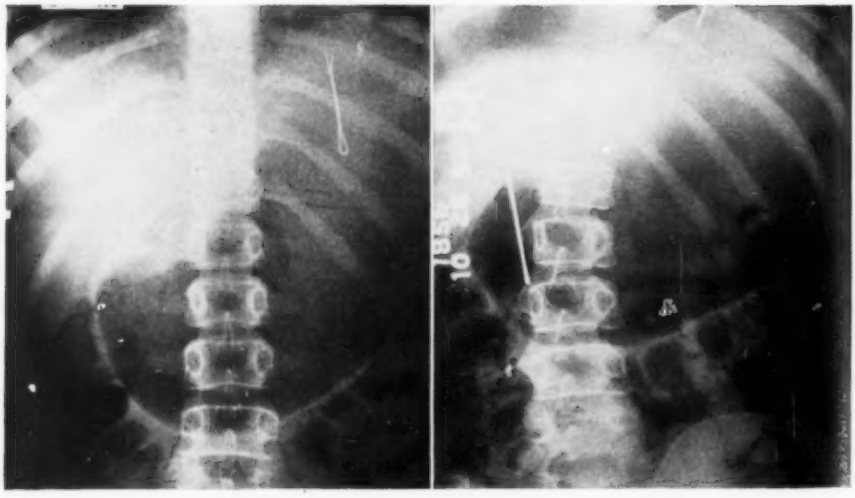


A. *B.*

Fig. 2.—(*For legend, see opposite page.*)

through a bottle. At one time we attempted to distend the stomach of infants by inserting a Levin tube and insufflating the air with a syringe. Under such circumstances the distention of the stomach was transitory, and the air entered the lesser bowel rapidly. The end result was a relatively poorly distended stomach and a lesser bowel pattern even more difficult to cope with than before the procedure had been started. When a carbonated beverage

A.



B.

Fig. 3.—*A*, A hairpin is present in the left upper quadrant. *B*, Same patient as *A*, after drinking 150 c.c. of a carbonated beverage. The hairpin moves freely from the fundus to the antrum with change in the position of the patient.

is used, the gastric dilatation usually persists for a sufficiently long time to obtain adequate serial abdominal roentgenograms over about a half-hour period.

Another useful field for gas contrast is the identification of ingested foreign bodies, as pointed out by Roberts.[2] Not infrequently a question arises whether the foreign body is inside or outside the stomach. By means of gas distention and films made in the anteroposterior and lateral projections it is possible to identify an object in relationship to the walls of the stomach. Such a case is illustrated (Fig. 3) in which a hairpin moved freely within the gas-distended stomach.

This technique is not as applicable to adults as to children. Dilatation of the stomach with carbonic acid gas, as a rule, is insufficient to aid in the visualization of the kidneys in adults because the degree of distention is such that the kidney areas are not covered by the stomach. Carbonic acid gas distention of the stomach does find a definite field of usefulness in the portrayal of the gastric cardia. We keep a supply of sparkling water available for this purpose, and if a question as to the configuration of the fundus arises, the examination is supplemented with erect stomach films after the ingestion of about 150 c.c. of sparkling water. We have been informed[1] that sparkling water contains from 4.5 to 5.0 c.c. of carbonic acid gas per cubic centimeter of liquid, thereby affording a slightly greater degree of distensibility than can be obtained with flavored beverages.[1] If an inadequate amount of gas in relation to the size of the stomach limits the examination, a Levin tube is passed and the stomach distended with air under fluoroscopic control.[3]

SUMMARY

The use of carbonated beverages at room temperature has been found helpful in the radiography of the kidneys and stomach in infants and children.

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METHEMOGLOBINEMIA IN AN INFANT

Associated With Application of a Tar-Benzocaine Ointment

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METHEMOGLOBINEMIA in infants has been reported frequently and has occurred unexpectedly from a variety of causes. Immediate recognition is often essential to avoid a fatal outcome. Proper treatment is usually so simple and successful that the condition must be thought of in any case of cyanosis without an obvious cause.

Methemoglobinemia may result from ingestion, inhalation, or absorption of many substances.[1, 2, 3] It has been reported as far back as 1886 to occur by absorption through the skin as a result of the use of diapers freshly stamped with aniline dye,[4] and similar cases have been reported since.[5, 6, 7] Shoe dye containing aniline or nitrobenzene has similarly caused methemoglobinemia via skin absorption.[8] However, despite a fairly wide search of the literature and correspondence with a few authorities on the subject, no report could be located of a methemoglobinemia associated with the application of therapeutic ointments. The only cases involving ointment resulted from the ingestion of an anti-gas preparation.[9]

The following is believed to be the first case reported where it appears likely that the ointment used in the treatment of an infantile eczema was the cause of methemoglobinemia, although the actual etiological constituent has not been definitely ascertained.

CASE REPORT

E. S., a male infant, aged 3 months, was admitted to the City Hospital on Nov. 12, 1954, suffering from a very extensive and severe eczema involving most of the body, face, and scalp, with associated marked pruritus.

The condition had been present since one month of age, gradually becoming worse, but with short periods of improvement. He was treated with several ointments by his family physician.

The infant had remained in good general health and gained weight.

He was born in a country hospital after a normal pregnancy and labor. Birth weight was 8 pounds 13 ounces. He was breast fed until one week before admission, when he was given a formula of evaporated milk 8 ounces, water 18 ounces, and corn syrup 2 tablespoonfuls. A multiple vitamin concentrate, six drops daily, was also given.

Family history was noncontributory, except that the mother had had a mild "eczema" off and on since 14 years of age. Four siblings were in good health.

Examination on admission disclosed a well-nourished, well-developed infant, weighing 13 pounds 14 ounces, normal except for the widespread eczema involving most of the body, face, and scalp. The lesions were dry and erythematous. No obvious infection was noted.

The hemoglobin was 85 per cent (13.2 grams); red blood count 4,500,000;

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white blood count 25,600; differential: polymorphonuclears 20.5 per cent, rhabdocytes 4.0 per cent, lymphocytes 42.5 per cent, eosinophils 27.5 per cent, basophils 0.5 per cent. Examination of the urine revealed albumin and sugar negative; microscopic: negative.

Treatment was given as follows:

(1) Pragmatar* ointment to scalp, t.i.d., after removal of crusts with mineral oil.

(2) Hydrocortisone 1 per cent in Eucerin ointment to face and right side of body and limbs.

(3) Derm cream,† a Canadian product, to the left side of the body and the left limbs, applied liberally at least twice a day, covered by linen and bandaged. After the first thirty-six hours, the skin was left exposed. This ointment contains, according to the manufacturer, crude coal tar 2½ per cent, titanium dioxide 7½ per cent, zinc oxide 7½ per cent, calamine (B.P.C.) 2½ per cent, cetyl trimethyl, ammonium bromide 1 per cent, and benzocaine 5 per cent, in a special water-soluble base.

(4) Terramycin 33.3 mg. intramuscularly was administered O.H. xii for three doses.

(5) Elixir of phenobarbital, 1 dram, was given two to three times daily.

Restraints were used to avoid scratching, and plastic sheets were used over the mattress.

Formula on admission was evaporated milk 12 ounces, water 18 ounces, corn syrup 2 tablespoonfuls, with added feeding of ripe banana and applesauce.

On the day after admission, a moderate diarrhea developed with loose yellow stools. Vomiting occurred once. Stools had been normal before this.

Regular feedings were discontinued November 14 and weak tea was offered. On the following day, a formula of evaporated skim milk and water, equal parts, was fed, with Appella Mush, 1 to 2 tablespoonfuls before each bottle; and on November 16, Arobon, 2 teaspoonfuls to 4 ounces formula was added. Kaopectate and neomycin,* 1 dram, q.i.d., were also given orally.

Diarrhea continued with five to ten loose stools daily. The infant, however, did not appear ill or dehydrated and maintained his weight.

The skin responded rapidly and equally well on both sides of the body, and on the face and scalp.

Stool culture, November 15, revealed growth of coliform and hemolytic coliform organisms.

On the morning of November 17, the fifth day after admission, about 10:30 A.M., the infant became cyanotic quite suddenly. Respirations appeared gasping but not rapid. Vomiting occurred once, and he appeared critically ill. He was immediately transferred to an oxygen tent and the ointment rapidly cleaned off, the last application having been one hour earlier.

The grayish blue cyanosis of methemoglobinemia appeared, typical of that seen frequently in infants under 2 months of age, given well water with a high nitrate content.[10, 11]

The water given to this infant was city water with a low nitrate content.

Methylene blue 1 per cent, 1.5 to 2 c.c., was injected into a scalp vein at 10:50 A.M. Within thirty minutes there was a marked improvement, and by forty-five minutes to one hour the infant was a welcome pink in color and appeared normal.

A specimen of blood was obtained with some difficulty a few seconds after the methylene blue was injected. It appeared chocolate brown, and was sent to the Provincial Laboratory at Regina, Saskatchewan, for methemoglobin determination. This was performed in about twenty-four hours and was reported as 55 per cent of the hemoglobin content. It was felt that doubtless the true methemoglobin was closer to 80 per cent or more at the time the infant was severely cyanotic. Furthermore, the methylene blue had been administered just before the specimen

*Smith, Kline and French.
†Ingram and Bell Ltd.

*Upjohn.

of blood was taken, and there was a delay of twenty-four hours in estimation.

The infant remained well. The bowel movements next day varied from formed to soft. The skin remained greatly improved.

On November 18 the hemoglobin was 77 per cent (12 grams); red blood count 4,060,000; white blood count 12,700; differential: polymorphonuclears 34 per cent, rhabdocytes 7.5 per cent, lymphocytes 41.5 per cent, monocytes 10 per cent, eosinophils 6.5 per cent, basophils 0.5 per cent. X-ray of the chest on the same day was reported to be negative.

DISCUSSION

This infant with severe atopic eczema confronted us suddenly with a severe cyanosis and anoxia resulting from methemoglobinemia. Fortunately, acquaintance with the picture of this condition resulted in prompt therapy with intravenous methylene blue, and a tragic outcome was averted.

The immediate impression was that the Derm Cream ointment applied liberally to 40 per cent or more of the body was the most likely cause of the methemoglobinemia.

The ointment contains 2½ per cent crude coal tar, and coal tar derivatives having frequently been incriminated, the crude coal tar was considered to be the most likely toxic agent here.

Coal tar is a by-product in the destructive distillation of coal, and contains the following constituents[12]: benzene, toluene, naphthalene, anthracene, xylene, and other aromatic hydrocarbons; phenol, cresol, and other phenolic bodies; thiopentene; ammonia, pyridine, and some other organic bases vary, the proportions depending on the method of producing the coal tar.

Despite an extensive search of the available American and English literature, no report could be found where crude coal tar caused methemoglobinemia. Crude coal tar is widely used as a most effective agent in the treatment of infantile and other eczemas and has been applied over large areas of the body. If it could cause methemoglobinemia, it is difficult to understand why no previous report has been made.

Different authorities advise that crude coal tar ointment should not be applied over 25 per cent,[13] and others, to over 50 per cent of the body.[14] Standard texts of pediatrics and dermatology discuss very briefly the toxic effects, and mention only photosensitization and phenol absorption with possible kidney damage. Brown and Tisdall[14] in their text state that the tar ointment they prescribe may be applied to at least one-half of the body surface without fear of toxic phenol absorption. Their ointment is very similar to Derm Cream and contains 2.5 to 5 per cent crude coal tar but Nupercaine 1 per cent instead of benzocaine.

Benzocaine 5 per cent is also present in the ointment used in this infant. Benzocaine is an aromatic amine, but the amino group is very stable, [15] as compared with aniline and its derivatives. It has never been reported as causing methemoglobinemia.

Hydrocortisone 1 per cent in Eucerin was applied to one-half the body three times daily. It was found that, due to the squirming of the infant, this ointment and the Derm Cream were intermixed over a wide area.

According to Selye,[16] the increase in capillary permeability caused by stress is largely prevented by adrenocortical extracts or ACTH. The spreading of intradermally injected dyes is acceler-

ated by adrenalectomy and inhibited by cortisone or procedures which cause ACTH discharge. This suggests that hydrocortisone did not increase absorption from the applied ointment.

Whether hydrocortisone, in combination with any of the substances used, may be responsible for the rise of a pathological process which could have caused the methemoglobinemia is not known.

The Pragmatar ointment contains 4 per cent crude coal tar distillate but was used only on the scalp and was not considered a factor in this case.

The diarrhea, which developed the day after treatment was instituted, improved rapidly after discontinuance of the Derm Cream. It seems unlikely that it was related to the methemoglobinemia, nor does it appear to fit the picture of so-called enterogenous methemoglobinemia,[1, 2, 3] an entity which is not wholly accepted.

Other previously described causes were considered. As is well known methemoglobinemia has been caused by sulfonamides, especially sulfanilamide. It has also been caused by phenacetin, acetanilide, aminophenols, aniline dyes, nitrobenzene, wax crayons, shoe dyes, potassium chlorate, bismuth subnitrate, nitrates, and many other substances.[1, 2, 3] None of the above could be incriminated in this case.

None of the medications used internally were suspect. These included Terramycin, Kaopectate with neomycin, and phenobarbital. City water with a safe, low nitrate content was used in the feeding. No freshly stamped linen was used. No other infants have been similarly and unexpectedly affected in this hospital. There was no reason to suspect the congenital or familial methemoglobinemia which has been described.

We feel that the coal tar-benzocaine ointment was the most likely factor in causing the methemoglobinemia.

We also considered that a project attempting to reproduce the condition in susceptible animals, with the use of the same ointment, would be valuable, but facilities for adequate animal research were not available. However, one kitten was shaved and coated daily with the Derm Cream and hydrocortisone 1 per cent in Eucerin. Methemoglobin estimations were performed spectroscopically every two days. The kitten became toxic and listless and was sacrificed on the seventh day, but no increase in methemoglobin was demonstrated.

SUMMARY

A case is described of methemoglobinemia in an infant with severe atopic eczema.

This infant, on the fifth day after treatment was initiated, became critically ill, cyanotic, anoxic, and almost died. Methylene blue, 1.5 to 2 c.c. of a 1 per cent solution intravenously, resulted in a dramatic cure.

The treatment of the eczema included application of an ointment containing 2½ per cent crude coal tar to almost one-half the body and 1 per cent hydrocortisone in Eucerin to the other half. The possibility that this ointment caused the condition is considered.

This case re-emphasizes that awareness and recognition of methemoglobinemia as a cause of unexplained cyanosis cannot be too strongly stressed, as proper treatment may be lifesaving.

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Prematurity or Sin?

Dec. 11. 1722. A Council of the Churches at Abington, viz of Milton, Dorchester, & the north part of Braintrey met & after Publick Hearing of the Case, . . . Judged Wm Hersey jun. & his wife to have been guilty of fornication before marriage. . . & the said Wm Hersey junr said that He never would deny that he had the Carnal Knowledge of her body before that day that they were married together: & by Sundry sworn evidences it was proved that their first Child had a full grown body Ripe for the birth & long hair & hard nails, & Cryd & fed well when it was first born, tho born but five months & nine days from its parents marriage, & the women made oath before Justice Edson & the Council before we went to the Meeting House, that they believed no Child ever attained to such ripenesse & perfections at 5 months & nine days from the Conception.

RECORDS OF THE FIRST CHURCH AT DORCHESTER 1636-1734. BOSTON, 1891.

JIMSON WEED (DATURA STRAMONIUM) POISONING IN CHILDHOOD

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IN METROPOLITAN areas of the United States one is not likely to be confronted with poisoning by *Datura stramonium*, Jimson weed, but accidental intoxication by this plant is not uncommon in rural areas of this country, particularly the eastern half. During the past five years at the University of Virginia Hospital, which services a large southern rural area, Datura has accounted for approximately 4 per cent of pediatric patients admitted because of ingestion of a toxic substance. Although distinctly less frequent than kerosene or salicylate intoxication, Datura has had about the same incidence as lead, barbiturates, alcohol, rodenticides, and insecticides as a source of poisoning during this period.

The alkaloids, hyoscyamine, atropine, and hyoscine, are contained in every part of the Jimson weed. Depending on the part examined, the amount will vary, but a value of 0.25 per cent has been found to be the minimum total quantity assayed.[1] The predominating alkaloid is hyoscyamine, with lesser amounts of the other two alkaloids. The symptoms produced by ingestion of the vegetation are not unlike those resulting from overdosage of these three alkaloids either singly or in combination. The plant is an annual one originally found in this country only in the southern states, but as early as 1797 it was described by Barton as having spread into Pennsylvania where it was looked upon as a curiosity.[2] Since then it has become rather generalized in its distribution throughout the States. Species of Datura are also found in most parts of Europe, Asia, Africa, and South America.

The plant, which may attain a height of 3 to 6 feet, has a fetid odor. The leaves are dark green, sessile, large, measuring up to 4 to 6 inches, pointed, angular, and have a deeply indented margin. The leaves have a bitter, nauseating taste. A five-lobed, white, trumpet-shaped flower, which blooms from May to July, is produced and develops into a four-valved spinous capsule containing many tiny, flattened, blackish-brown seeds attached to a central placenta.

Since the plant grows wild around dung-heaped barnyards, along roadsides, ditches, and other marginal areas, it is readily available for a child to taste or eat. The leaf is frequently used in home medicinals as a tea. It is this home medicinal use that has accounted for the majority of our cases.

Jennings[3] has reviewed some of the long history of poisoning from Jimson weed and mentions a group of men[4] under Captain John Smith who, during the Bacon Rebellion in 1676, ate

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the leaves in a salad and exhibited marked symptoms shortly thereafter. These are probably the first recorded cases of Datura poisoning in this country. Professor Barton later mentioned the cases of three British soldiers who ate Jimson weed, having mistaken it for "lamb's-quarters" *(Chenopodium album)*. "One became furious and ran about like a madman. A second was seized with genuine tetanus of which he died. The fate of the third is not remembered." The weed has been used in Russia[5] for increasing the intoxicating effect of beer and has a long history as being used criminally from the hashish eaters (assassins) in the time of Omar Khayyám to the present day in Europe.

Jimson weed poisoning in children was not uncommon a century ago,[4] and it would appear that poisoning from this plant is more common now than a review of the literature would lead one to suspect. Since the symptomatology is so characteristic as to lead to prompt diagnosis when there is a high index of suspicion, the following cases appear worth reporting in order to reemphasize Jimson weed as a ready source for accidental poisoning in childhood.

CASE REPORTS

A Negro family which had been suffering from persistent upper respiratory infections felt that a laxative would be what they needed to help themselves over this temporary physical inconvenience. They were in possession of some dried leaves which had been sent to them by a well-meaning northern relative. The leaves were supposed to have a laxative effect if used as a tea. An infusion was prepared by putting an unknown quantity ("fingerful") of the leaves into a quart of water and boiling until it was one-half the original volume. The drinking of this therapeutic brew soon produced a group that could vie with the Mad Hatter's tea party, for the leaves from which the tea had been brewed were those of *D. stramonium* or Jimson weed. The first four patients described here received their toxic dose from this therapeutic tea, while two other adult members were also affected but are not described.

CASE 1.—L. D., a 6-year-old Negro male, drank about 2 ounces of the brew. Within thirty minutes he complained of dizziness and shortly became excited to the point of hilarity. There was rapid breathing noted by other members of the family and the patient appeared to have lost his memory. When first seen at the hospital, his pulse was 130 per minute, respirations 28 per minute, and body temperature 100.4° F. The pupils were dilated and fixed, the mouth dry, the lips red, and a generalized blush was present. The patient picked at himself and imaginary objects in the air and soon became so hyperactive that restraints were required. He was given pilocarpine and sedation on two occasions and ½ ounce of magnesium sulfate by mouth. His recovery was rapid and uneventful.

CASE 2.—L. A., a 13-year-old Negro male and brother to Case 1, drank 2 ounces of the Jimson weed tea. When seen at this hospital, the temperature was 98.6° F., pulse 140 per minute, respirations 28 per minute, and the blood pressure 95/58. He had a facial blush, dry skin, dilated pupils, frequent nonproductive expectoration, rapid, incoherent, irrelevant speech, and random picking at himself and imaginary objects in space. He later became delirious and required restraints. He improved on symptomatic treatment and made an uneventful recovery.

CASE 3.—E. A., an 8-year-old Negro male and brother of Cases 1 and 2 also drank about 2 ounces of Jimson weed tea. When seen at the hospital he was found to have a temperature of 100° F., pulse of 100 per minute, res

pirations of 24 per minute. The pupils were dilated and did not react to light; there was a generalized blush to the skin which, along with the mucous membranes, was dry. The patient was very excited, irritable, and jabbered incoherently. After being treated with morphine in small amounts and pilocarpine, he became rational, but the pupils remained dilated for six days. His recovery was complete.

In addition to these children two adults and one young adult were admitted to the medical service for similar difficulties. They were able to report that within thirty minutes vision became hazy, then vertigo, xerostomia, weakness of extremities, and clouding of the sensorium ensued. The latter progressed to complete loss of memory. All made uneventful recoveries.

CASE 4.—J. F. B., an acutely ill 3-year-old Negro male, was admitted to the hospital in an unconscious state. The first sign of illness had been irritability followed by a convulsion and finally unconsciousness. When seen at the hospital, the temperature was 101.6° F., the pulse 84 per minute, respirations 22 per minute. There was a generalized blush to the skin, widely dilated pupils, and a distended bladder and abdomen. After regaining consciousness, the patient was very irritable and developed involuntary movements of the extremities. He gradually improved with supportive measures and made a complete recovery. Later a definite history of Jimson weed ingestion was obtained but the quantity was unknown.

CASE 5.—F. S. H., a 4-year-old white male, awakened from a nap with crying, thrashing of the legs, and failure to recognize his parents. He was brought immediately to the hospital where the temperature was found to be 102° F., the pulse 96 per minute, respirations 24 per minute, and the blood pressure 140/60. He was extremely agitated, disoriented, and screamed loudly. An erythematous macular eruption imposed upon a generalized blush of the skin was noted and circumoral pallor described. The pupils were widely dilated and reacted sluggishly to light and accommodation. The throat and conjunctivae were slightly injected. He was treated with intravenous fluids, antibiotics, and phenobarbital. His recovery was uneventful. Later it was learned that the patient had eaten Jimson weed and the plant was brought in for identification.

CASES 6 AND 7.—H. W. and L. H., both 5-year-old white males, were brought to the hospital after having drunk an unknown quantity of Jimson weed tea. Prior to arrival both had been given twenty drops of ipecac and soda with sweet milk, but only one of the boys, L. H., had vomited. The emesis occurred four hours after receiving the emetic. When seen, L. H. had a temperature of 99° F., pulse 100 per minute, respirations 30 per minute, while H. W. had a temperature of 100.2° F., pulse of 100 per minute, respirations 24 per minute. When seen, L. H. was said to have been lethargic, while H. W. was excited. Both boys had dilated pupils and dry, flushed skin. Both were treated by forcing fluids and H. W. received one small dose of Seconal. The following day H. W. was slightly hyperactive but both boys made excellent recoveries.

DISCUSSION

The symptoms common to all of these cases are the dilated pupils, the marked flush of the skin, and the central nervous system disturbances which early manifests itself by marked excitability in every case. It has previously been stated that a maniacal form of the poisoning is more likely to occur from ingestion of the seed, whereas a comatose form is usually seen when the leaves are the causative agent[6]; however, this would not appear to be true in any of these cases. It would rather appear that the initial reaction is one of hyperirritability and delirium which may progress to con-

vulsions and terminate in coma, depending upon either the amount of drug taken and/or individual idiosyncrasy to the drug.[7] Other disturbances seen were involuntary picking movements, incoherent speech, and, where possible to ascertain, loss of memory. Other symptoms seen due to the parasympathetic depressant action of the alkaloids in Jimson weed were tachycardia, xerostomia with expectoration, bladder distention, visual disturbances from poor accommodation, and injection of the throat and conjunctivae. The acute symptoms usually subside within twenty-four to forty-eight hours but mydriasis may persist for a week or more.

When ingestion of the plant is known or when the patient is seen early and the ingestion of Datura is suspected, gastric lavage with tannic acid (strong tea) or dilute tincture of iodine (30 drops in a pint of water) should be done to precipitate any alkaloid remaining in the stomach. If the patient is seen late, as is usually the case, this procedure is of questionable value. During the maniacal or delirious stage, sedation with short-acting barbiturates or paraldehyde should be employed in order to prevent self-injury or convulsions. As little of these drugs as is feasible should be used since central nervous system depression may occur and require the use of benzedrine or other central stimulating drugs. When dry mouth, tachycardia, or other sympathomimetic responses are distressing, pilocarpine or neostigmine may be used in an effort to control the symptoms. Parenteral fluids should be used judiciously in order to maintain proper water and electrolyte balance.

Since the most usual method of ingestion is by teas, infusions, or by accident with whole leaf or seeds, it is very difficult to determine the exact amount that any one patient receives. However, on the basis that 10 mg. of atropine[1] is usually a fatal dose of atropine in a child, and since hyoscyamine, the principal alkaloid of Jimson weed, is somewhat more toxic than atropine, the fatal dose would appear to be in the neighborhood of 4 to 5 Gm. of the crude leaf or seed. Much smaller quantities are capable of producing distressing and serious symptoms.

SUMMARY

Jimson weed intoxication is not an uncommon cause of poisoning in children. The signs, symptoms, and treatment are discussed and a rough estimate of the fatal dose is made. Seven cases of Jimson weed intoxication are reported.

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VISCERAL PAIN ASSOCIATED WITH ABNORMAL ELECTROENCEPHALOGRAPHIC FINDINGS IN PATIENT AND SIBLINGS

Report of One Case of Abdominal Epilepsy

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THE following report is that of a 10-year-old white female who was seen in the emergency room and outpatient clinic on several occasions over a period of three weeks with chief complaint of abdominal pain. Physical examinations and laboratory studies were normal and the true nature of the problem was not appreciated until it was noted that following one episode of severe abdominal pain, the patient was slightly disoriented:

L. M., a 10-year-old school girl, was apparently well except for a hearing difficulty until three weeks prior to admission when she began to have generalized, intermittent, sharp abdominal pains. Each episode of pain lasted "several minutes" and was of sufficient degree to force the child to lie down and draw up her knees on the abdomen. The pain was accompanied by nausea but no vomiting or salivation. The pain frequently followed eating or drinking, and as a result the child had decreased her food intake. The episodes of pain had increased both in intensity and frequency until the patient was experiencing three to four attacks daily. According to the mother, the child frequently cried out with pain and refused to move during an attack. The parents felt that the patient remained completely conscious and oriented during these episodes. The attacks did not seem to come at any specific time of day. On occasion, the child would awaken in the morning feeling nauseated, and, by the time she was ready to leave for school, she would be experiencing severe pain. At other times it appeared that attempts to eat breakfast initiated the feeling of nausea and pain. The child slept well at night and had never been aroused from sleep because of abdominal pain.

The patient is a happy child and plays well with her siblings and schoolmates. She is not timid or inhibited in speech or play. However, she does not do well in her schoolwork. The mother feels this is due to a hearing loss which was associated with frequent bouts of otitis media during childhood. Serial audiometric studies at this hospital were consistent with an air conduction type deafness.

The patient is the product of a normal delivery and an uncomplicated prenatal and postnatal course. She has a normal developmental history. She has had no head injuries, convulsive episodes, or loss of consciousness. There is no history of meningitis, encephalitis, poliomyelitis, severe febrile illnesses, abnormal neurological symptoms or related diseases. She has had the usual childhood diseases

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of measles, mumps, and tonsillitis without abnormal severity of symptoms or sequelae.

The physical examination of L. M. revealed no abnormalities other than moderate deafness. The neurological examination revealed no significant deviation from normal. She was rather small and immature physically in relation to chronological age.

In the hospital, the patient was placed on bed rest and a regular diet during the investigational work-up. The complete blood count and urinalysis were normal. The sedimentation rate, corrected, was 8 mm. per hour. The cephalin flocculation was negative; icterus index was 5 units, serum bilirubin was 0.375 mg. per cent; thymol turbidity was 2.25 units. The stools were negative for blood, ova, and parasites. Serum amylase was 120 Somogyi units. A fasting blood sugar was 84 mg. per cent. Spinal fluid pressure and chemistries were normal. Repeat audiograms revealed an air conduction type of hearing loss. Gastrointestinal series and barium enema studies revealed no abnormality. Repeated electroencephalograms with and without Metrazol were found to be grossly abnormal and compatible with a convulsive disorder.

During fifteen days of hospitalization, the patient's temperature, pulse, and respiration were normal at all times and she had no episodes of pain. She slept well and ate well. On the morning of discharge, she did not eat breakfast and complained of nausea but no pain. She was placed on phenobarbital gr. ¼ three times daily. Follow-up of this patient since discharge reveals that she has had no further abdominal symptoms.

The family history is negative for familial diseases such as nervous disorders, insanity, and epilepsy. One sibling, T., a 14-year-old girl, had similar abdominal symptoms of one year's duration. Three years ago, an exploratory laparotomy was performed with the removal of the appendix and since then T. has been free of abdominal symptoms. The following is the pathologist's report of the surgical specimen:

"Gross: Specimen consists of a formalin-fixed appendix and a portion of the meso-appendix measuring 9 by 1.5 by 0.7 cm. It is slightly kinked on itself in the proximal portion. The serosal surface is not injected, nor is it covered with fibrin. At the tip, the lumen is dilated and contains a soft, brown fecalith. The lumen throughout the remainder of the appendix contains soft, fecal material. Three routine sections, diagnosis: Appendicitis, chronic focal (fecalith)."

Electroencephalographic findings on members of the family were as follows: (1) Father, aged 51, normal tracing, (2) Mother, aged 50, normal tracing. (3) Sister "M," aged 13, normal tracing. (4) Sister "T," aged 14, paroxysmal bursts of high amplitude slow waves, symmetrical, seen in all leads, but predominantly in parieto-occipital leads. Early build-up on hyperventilation stimulation and sustained posthyperventilation. Pattern compatible with convulsive disorder. (5) Brother "T," aged 11, early build-up of high voltage slow waves occurring in bursts, symmetrically in all leads during stimulation by hyperventilation. Noted were two episodes of transient jerking of arms and legs at the end of hyperventilation and at one and one-half minutes posthyperventilation.

DISCUSSION

In 1944, Moore[1] was the first to describe a case of paroxysmal abdominal pain as a form of focal epilepsy. Prior to that time, Gower,[2] Patrick and Levy,[3] and Bridge[4] pointed out the significance of abdominal complaints as a frequently described aura in epilepties. Klingman and associates,[5] in describing twelve cases, inferred that abdominal pain was related to epilepsy. Since 1944, Moore[6]

has studied eighteen additional cases; Hoefer and co-workers[7] have reported thirty-one cases; Livingston[8] reported on fourteen; Blumberg[9] and Hernandez R.[10] each reported on one additional case.

It is interesting to note that the older sister, T., who had the history of abdominal pain and a relatively normal pathology report on the removed appendix, had an abnormal electroencephalographic pattern compatible with a convulsive disorder. In previously reported cases of abdominal epilepsy the disorder was rarely found in two siblings.

The younger brother, who displayed no clinical signs of epilepsy, also had an abnormal electroencephalographic pattern. He had two transient seizures during the running of the electroencephalogram and this validated the designation of his abnormal electroencephalogram as epileptic in nature.

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AMEBIC ABSCESS OF THE LIVER IN AN INFANT

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HEPATIC abscess as an important complication of amebiasis is fairly common in adults but appears to be relatively rare in infancy and childhood judging by the small number of case reports in the literature. General discussions available on the process in adults include only a few cases in children. In their excellent review article on the subject, Ochsner and associates[1] presented a series of 139 cases, only two of which occurred in individuals less than 9 years of age. Perusal of the literature indicates that most of the reported cases in infancy and childhood have occurred outside of the United States in widespread areas of the world. Niblock,[2] from India, reported a case in an 11-month-old infant, Sweet[3] a case in a 5-year-old Chinese girl, and Ludlow[4] included three cases in children in his series of 160 cases collected in Korea.

Because of the uncommon occurrence of amebic abscess in the liver, especially in this country, another case is presented.

CASE REPORT

History.—A 17-month-old white male infant was admitted to the Children's Medical Center, Dallas, Texas, with fever. Ten days prior to admission, the patient had a measleslike rash, which had cleared. Four days before admission, the patient developed fever ranging from 102° to 105° F. (rectally) which persisted, associated with mild cough, despite administration of penicillin. No history was given of vomiting, cyanosis, or convulsions. There was no suggested contact with parasitic infestation. The father had not served in the Armed Forces during World War II.

Physical Examination.—A well-developed and well-nourished white male infant appeared to be acutely ill. Temperature was 101.2° F. (rectal); pulse 140; respirations 30 to 36 per minute. Numerous rhonchi were heard over both lung fields with the breath sounds roughened over the left upper lung field posteriorly. No murmurs were heard, and the cardiac rhythm was regular. The abdomen was distended and tympanitic to percussion. The liver and spleen were not thought to be enlarged, although palpation was done through a tight abdominal wall.

Course in Hospital.—At the time of admission, it was felt that this patient was in the convalescent stage of measles with bronchopneumonia as a complication. He was placed on penicillin, 50,000 units every three hours; oxygen therapy was instituted for cyanosis, and aspirin and cool sponges were administered for fever. The hemoglobin was 6.7 grams per cent; the red cell count was 2.9 million per cubic millimeter, and the white cell count 29,000 per cubic millimeter of blood. During the next two days he made little response to therapy, as he ran a septic type of fever with persistent abdominal distention and cyanosis. He began passing several stools a day, but these were soft and yellow and were not examined for parasites. Sulfadiazine and dihydrostreptomycin were added to the therapeutic regimen. Fluids were given as indicated, and a small blood transfusion was given each day. On the third hospital

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day, the patient deevloped a tachycardia and dyspnea, associated with severe cyanosis, and for the first time the liver edge was palpated 4 cm. below the costal margin despite the continued abdominal distention. Wangensteen suction was started with some clinical improvement, although the liver edge did not recede. For the first time, a change was noted in the gross character of the stools—loose, even liquid, green stools were admixed with variable amounts of mucus. On the fourth hospital day the baby passed seven recorded stools, but with no blood noted, and benzidine test on a stool specimen was negative. The abdominal distention persisted and did not appear to be relieved by Wangensteen suction. The liver edge progressed further downward and was definitely at the level of the umbilicus by the fifth hospital day. The respiratory distress had subsided gradually, and the heart rate had come down to 164, but mild generalized cyanosis persisted. On the fifth hospital day, the abdomen was noted to be greatly distended, and the right upper quadrant was seen to bulge forward and laterally. A film of the abdomen and excretory urogram gave fair visualization of the urinary tract with no significant distortion of either side. In the supine films the liver appeared to be quite large. Despite the patient's poor clinical condition, an exploratory laparotomy was done on the sixth hospital day. The anterior aspect of the right lobe of the liver seemed edematous, as it pitted on pressure. Two small plaques of fibrin near the gastrohepatic ligament were seen on the inferior surface of the liver. The abdominal wall was closed without drainage. Pathological examination of the fibrin plaques revealed groups of neutrophils admixed with fibrin; no specific organisms were seen.

Within only a few hours postoperatively, the patient was noted to be jaundiced, and the urine was found to contain bile and an increased amount of urobilin. Tachypnea, fever, and lethargy were prominent clinically. On the seventh hospital day, films of the abdomen showed a large mass in the right upper abdominal quadrant, elevation of the right leaf of the diaphragm, and pleural thickening in the lower half of the right lung field laterally. The stools at this time were loose, watery, dark green in color, and contained not only mucus, but small traces of blood. Multiple stool examinations for ova or parasites during the hospital course were negative. Because the mass in the right upper quadrant had continued to increase in size, the patient was again operated upon. Under local infiltrative anesthesia an incision was made over the dome of the swelling. The liver was aspirated of approximately 15 c.c. of an odorless, dark brown, watery fluid. Pus cells but no specific organisms were seen in the gram-stained smear; culture showed no growth. Examina-

Fig. 1.—Longitudinal section through the mid-portion of the right lobe of the liver demonstrating cavitation.

tion of the cell block prepared from the fluid aspirate showed much necrotic debris, including necrotic liver tissue, a few red cells, and pus cells, but no organisms. The following day aspiration done at a prepared site over the liver obtained 135 c.c. of a slightly viscid, brownish-red fluid, and a Penrose drain was inserted. The patient made little response to surgical drainage, and his general condition rapidly became worse. Terminally, respirations became labored; tachycardia and gallop rhythm developed. Death came on the eleventh hospital day.

Necropsy.—The findings of importance in this markedly jaundiced infant were largely confined to the abdomen. About 250 c.c. of dark yellow, clear fluid escaped from the peritoneal cavity, and fibrinous adhesions were seen over the peritoneal surfaces. The liver was considerably enlarged (weight 1,800 grams), elevated the diaphragm, and extended below the right costal margin for 12 cm. or more, easily filling the right half of the abdominal cavity. The dome was bound to the diaphragm by means of fibrinous adhesions. Pitting edema was demonstrable over the surface of the right lobe, which was almost completely shelled out by a large cavity with only a narrow wedge being spared inferiorly (Fig. 1). The central area of this cavity contained 200 c.c. or more of a cloudy, dirty, brownish-red, thick fluid with small flecks of digested tissue therein. In microscopic section an amebic abscess was seen to be lined by a zone of granular necrotic liver tissue with dead organisms identified as *Endamoeba histolytica* in the periphery. The junction zone in the abscess wall between necrotic and viable liver cells was an uneven one, with a narrow rim of acute and chronic inflammatory cells, including many neutrophils. Between the thickened liver capsule and the central part of the abscess there was extensive hemorrhagic necrosis of the liver tissue in the dome of the right lobe of the liver.

The right pleural cavity contained 150 c.c. of brownish-yellow, clear fluid with a minimal amount of fibrin on the lateral and inferior pleural surfaces. Microscopic sections taken from the lower lobe of the right lung showed focal areas of necrosis, including several subpleural lobular units. In those areas alveolar lumens contained red blood cells, fluid, and small groups of amebae, with an inflammatory cell component at a minimum. The length of the large intestine was diffusely studded by numerous small ulcers of a "water-bottle" configuration seen in section to be flask-shaped in outline and containing many amebic organisms. The appendix, particularly, showed numerous acute ulcers loaded with organisms, and at one point microscopic penetration of the wall was seen with organisms extending from lumen to serosa. The kidney showed the changes associated with bile nephrosis.

Comment.—This patient presented a complicated problem from the beginning, as he was recovering from a virus infection. Though it was recognized that amebiasis was a possibility, no organisms were demonstrated in multiple stool examinations. The delay in establishing a correct diagnosis until hepatic abscess was obvious naturally lessened chances of obtaining satisfactory surgical result. Then, too, the rarity of this process in an infant was disarming.

SUMMARY

A case of acute amebic abscess of the liver with associated pneumonitis and intestinal amebiasis is presented in a white male infant, aged 17 months.

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Medical Progress

TONICITY AND ITS CLINICAL APPLICATION TO PARENTERAL FLUID THERAPY

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DEFINITION OF TERMS

OSMOSIS, osmotic pressure, osmolarity, osmols, milliosmols, isotonic, hypertonic, hypotonic, equivalents, milliequivalents—what are they? What do they mean? Why are they of importance? These are all terms that will be encountered constantly by those persons who are interested in the administration of parenteral fluids, either clinically or experimentally. It is the purpose of this communication to provide a working knowledge of the meaning of these terms.

OSMOSIS

Osmosis is the term which refers to the unequal rates of passage back and forth through a membrane of the contents of different solutions separated from each other by the membrane. It should be remembered that in talking about solutions, reference is made not only to the water in the solution which acts as the solvent, but also to the various substances that are dissolved in the water. (These dissolved substances are often referred to as solutes.)

The majority of membranes that occur in the body are a type of membrane spoken of as "semipermeable" membranes; that is, these membranes permit the free passage of certain chemical molecules, but partially or completely inhibit the passage of other molecules. Typical examples of semipermeable membranes in the body would include the walls of capillaries and the walls of the individual body cells. As an aid to the understanding of osmosis, referral to Figs. 1 and 2 will be helpful.

Figs. 1 and 2 illustrate a flask which has a barrier down the middle. The bottom portion of the barrier is a semipermeable membrane. This membrane (for the purpose of this illustration) is one which will permit the free passage of water particles or, more specifically, water molecules, but will not permit the passage of dextrose molecules. Fig 1 demonstrates a situation in which equal amounts of two different dextrose in water solutions are placed on either side of the membrane. It is to be noted that the dextrose solution on side A has a lesser amount of dextrose in it than the solution on side B. Thus, the dextrose solution on side B is more concentrated than the solution on side A.

If the flask pictured in Fig. 1 is set aside for awhile, the process of osmosis will occur. Fig. 2 represents a cross-section of the same flask pictured in Fig. 1 after osmosis has occurred. When the two figures are compared, a very interesting situation

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is to be noted, namely, that the level of the solution on side A has fallen and the level of the solution on side B has risen.

How did this come about? All of the chemical particles in any solution are moving about in a random fashion. This means that some of the particles in the solution will be striking each other and the walls of the container, and some will even be flying off in the air above the surface of the solution. In the pictured solutions, water and dextrose particles will be striking each other, the walls of the beaker, and the semipermeable membrane. In this case, the water particles can pass through the membrane, but the dextrose particles cannot. The solution on side A has more water particles and less dextrose particles per unit of volume than does the solution on side B. Not only are there less water particles per unit of volume on side B, but there are more dextrose particles per unit of volume which can get in the way of the water particles. Therefore, according to the laws of probability, more water particles will be striking and passing through the membrane from side A than from side B. Thus, over a period of time, two things will happen:

1. There will be a decrease in the total number of water particles on side A and an increase in the total number of water particles on side B, which explains the decrease in the amount of solution on side A and the increase in the amount of solution on side B.

2. The concentration of the two dextrose solutions will change in such a fashion that the solution on side A will become more concentrated and the solution on side B will become less concentrated.

Theoretically, under ideal conditions, both solutions should eventually contain the same number of water and dextrose particles per unit of volume, and just as many water particles should be passing through the membrane from side A to side B as are coming from side B to side A. This does actually occur with time, and when it does the process of osmosis will no longer be occurring. (It is to be remembered that osmosis refers

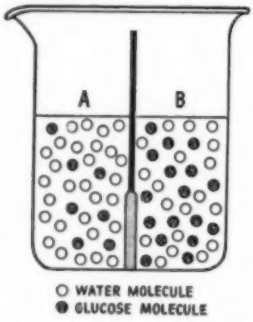

Fig. 1.—Demonstrates a flask in which equal amounts of two different dextrose and water solutions have been placed on either side of the membrane. The dextrose and water solution on side A is less concentrated than the dextrose and water solution on side B.

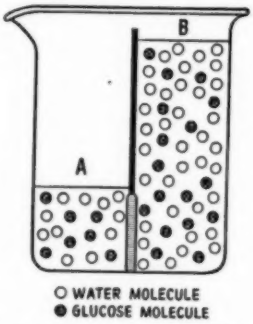

Fig. 2.—Represents a cross-section of the same flask pictured in Fig. 1 after osmosis has occurred. It is to be noted that the level of the solution on side A has fallen and the level of the solution on side B has risen. The solution on side A has become more concentrated and the solution on side B has become less concentrated.

to the *unequal* rates of passage back and forth through a membrane of the particles of different solutions separated by that membrane.) *Osmosis*, for our purposes, might be thought of as the "attracting" or "drawing" of water by concentrated solutions on one side of a semipermeable membrane from dilute solutions on the other side of the membrane. It is entirely dependent on the relative concentration of the dissolved particles that will not pass through the membrane separating the solutions.

OSMOTIC PRESSURE

The "attracting" or "drawing" power of any water solution can be determined by comparing the "drawing" power of that solution to that of pure water. A pure-water solution, of course, would have no "drawing" power in relation to another pure-water solution. The "drawing" power of a solution is called the osmotic pressure of that solution. The unit of osmotic pressure used in medicine is the *osmol*.

OSMOL

What is an *osmol?* For our purposes, an *osmol* may be defined as the *osmotic pressure* produced when one gram-molecular weight of any nonelectrolyte substance is dissolved in 1,000 ml. of pure water under certain specified conditions of temperature and atmospheric pressure. (When one gram-molecular weight of a substance is dissolved in 1,000 ml. of water, the solution is said to contain one mol of the substance per liter. Thus, the word osmol is derived from the words osmosis and mol.) There are several items in this definition that need to be explained.

What is a *gram-molecular weight?* All of the chemical elements in the universe have been assigned a weight called an atomic weight. The atomic weight of any element is the number that represents the weight of an atom of that element as compared with the number 16, which has been arbitrarily selected as the number to represent the weight of an atom of oxygen. The *gram-molecular weight* of any compound or element is thus defined as that weight in grams of that substance which contains the same number of molecules or particles as the number of atoms in 16 grams of oxygen. Therefore, *gram-molecular weights* of all substances will contain exactly the same number of molecules or particles, and an *osmol* of any substance will exert exactly the same osmotic pressure as any other substance. Likewise any mixture of substances that contains the same number of particles or molecules as the number of atoms in 16 grams of oxygen, will exert an osmotic pressure of one *osmol* when the mixture is dissolved in one liter of water.

Why the word "nonelectrolyte" in the definition of osmol? As will be remembered from the illustration of osmosis, the number of particles in a solution is the all-important factor in determining the osmotic pressure of that solution. Electrolytes are compounds that ionize when placed in solution. For instance, table salt is a compound composed of sodium and chloride. When a molecule of sodium chloride is placed in solution, it separates into sodium and chloride ions, and instead of there being one particle, a molecule of sodium chloride, there are two particles, a sodium ion and a chloride ion. Therefore, a *gram-*

molecular weight of an ionizable compound when dissolved in water, if the compound is completely ionized, will provide twice as many particles as one *gram-molecular weight* of a nonionized substance, and will have twice the osmotic pressure as the solution of the noneelectrolyte.

MILLIOSMOL

A *milliosmol* is the osmotic pressure that is produced by 1/1,000th of an osmol.

OSMOLARITY

Osmolarity is the term that refers to the number of *osmols* or *milliosmols* contained in a unit volume of solution. The unit volume of solution used in medicine is the liter or 1,000 ml. The milliosmol is the unit of osmolarity used most frequently in medicine.

OSMOTIC PRESSURE EXERTED BY ONE OSMOL

How much osmotic pressure does a solution containing one osmol of a substance per liter exert? A solution containing one osmol per liter exerts a pressure that is equal to about 22.4 atmospheres. One atmosphere is equal to a pressure of about 15 pounds per square inch. Thus, the solution would have a pressure of about 336 pounds per square inch.

Another illustration may help to further visualize the concept of osmotic pressure. Suppose in the flask pictured in Fig. 1, that one liter of pure water was placed on side A and one liter of dextrose-in-water solution containing one osmol of dextrose per liter was placed on side B. Further imagine that the level of the solutions was exactly even with the top of the flask, and that a water-tight cover was snugly fitted over side B. It would take a pressure of 336 pounds per square inch applied to the lid to keep the level of the solution on side B at the same level as that of pure water on side A. Thus, the dextrose solution on side B would have a "drawing" power equivalent to a pressure of 336 pounds per square inch.

TONICITY—ISOTONIC, HYPERTONIC, HYPOTONIC DEFINED

It now becomes possible to define the terms *isotonic, hypertonic* and *hypotonic*. A solution is said to be isotonic when compared with another solution if both solutions contain the same number of milliosmols. A *hypotonic* solution is one that contains a smaller number of milliosmols per unit of volume when compared with another solution. A *hypertonic* solution is one that contains more milliosmols per unit of volume when compared with another solution. In medicine, when a solution is said to be isotonic, it is usually meant that the solution contains the same number of milliosmols per 1,000 ml. as is contained in 1,000 ml. of blood plasma.

LABORATORY METHODS FOR DETERMINING OSMOLARITY

There are several laboratory methods for determining the osmolarity of any particular solution. The most important and commonly used methods consist in determining either the freezing point or the boiling point of the solution and then comparing them to those of a solution of pure water. It is a chemical fact that the addition of particles to a pure-water solution will depress the freezing point and raise the boiling point of that solution. Furthermore, elevation or depression is dependent upon and directly proportional to the number of

particles in solution. Therefore, one osmol or any given fraction of an osmol of any substance or mixture of substances will either raise the boiling point or depress the freezing point of a water solution to exactly the same degree. One osmol will raise the boiling point of a water solution by 0.515° C. and will depress the freezing point by 1.86° C.

It should now be apparent that it is not necessary, for our purposes, to know the actual value of osmotic pressures, but only to know the number of milliosmols present in any solution in order to compare its osmolarity with that of another solution.

In clinical and experimental medicine, the parenteral and body fluids concerned are not usually of the simple type described in the illustration. They are all water solutions. However, there are usually a number of different compounds dissolved in the water. The membranes in the body are also somewhat more complex. Not only will water go through most of the membranes, but many of the dissolved compounds will also do so to a greater or lesser degree. Despite this increased complexity of body fluids, the general principles described above are all valid.

Osmosis and osmotic pressure are among the most important processes and forces respectively that exist in the body, for in many instances it is by means of them that water, electrolytes, and other important compounds in the body pass in and out of cells and in and out of capillaries.

EQUIVALENTS AND MILLIEQUIVALENTS

Equivalents and *milliequivalents* are also terms that are used frequently. There exists some confusion in many persons' minds as to the difference between milliequivalents and milliosmols. A recent paper by Snively and Wessner[1] contains a very lucid description of the milliequivalent. The pertinent portions of this paper will be quoted verbatim:

> The body fluids contain chemical substances, chief among which are the "electrolytes." Electrolytes are substances which become ionized, that is, develop an electrical charge in water.
>
> Certain substances develop a positive charge and are known as "cations." Others develop a negative charge and are designated as "anions." Taking as an example the familiar sodium chloride, in the body fluids sodium is ionized and develops a positive charge and is, therefore, a cation. Chloride develops a negative charge and is, therefore, an anion. The sodium ion, which is positive, can react with the basic hydroxyl ion, which is negative. The chloride ion, which is negative, can react with the acidic hydrogen ion, which is positive. The sum of cations must equal the sum of the anions in the body fluid in order that electrical equality be maintained.
>
> The plasma contains the cations sodium, potassium, calcium and magnesium, and the anions chloride, bicarbonate, proteinate, phosphate, sulfate and organic acids. The interstitial fluid contains as its cations, sodium, potassium, calcium and magnesium, and as its anions chloride, bicarbonate, phosphate, sulfate, organic acids and proteinate. Within the cells are the cations potassium, sodium, magnesium and calcium, and the anions phosphate, proteinate, chloride, sulfate and bicarbonate.
>
> The unit of measurement of electrolytes is the milliequivalent, which expresses the chemical-combining power of an electrolyte.
>
> The older method of expressing electrolytes in terms of weight is outmoded. One would not compare the engine of an airplane to that of a locomotive on the basis of gross weight. For example, a locomotive that weighs 230,000 pounds has only 1,500 horsepower, while a certain airplane weighing about 45,000 pounds has 4,800 horsepower. Similarly, protein in terms of milligrams per 100 ml. weighs 6,500 mg., while it has a

TABLE I. MILLIEQUIVALENT AND MILLIOSMOL DISTRIBUTION AND CONTENT PER LITER OF SOME COMMONLY USED SOLUTIONS

SOLUTION	ROUTE OF ADMINISTRATION	ELECTROLYTES IN MILLIEQUIVALENTS/LITER								CARBOHYDRATE		TOTAL MILLI-EQUIVALENTS PER LITER	TOTAL MILLI-OSMOLS PER LITER
		NA^+	K^+	CA^{++}	MG^{++}	CL^-	$LACTATE^-$	$HPO_4^=$	AMINO ACIDS & PEPTIDES	GRAMS PER LITER	MILLI-OSMOLS PER LITER		
Normal saline	IV and subcutaneous	154	–	–	–	154	–	–	–	–	–	308	308
M/6 sodium lactate	IV and subcutaneous	167	–	–	–	–	167	–	–	–	–	334	334
Darrow's solution	IV and subcutaneous	122	35	–	–	104	53	–	–	–	–	314	314
Lactated Ringer's	IV and subcutaneous	130	4	3	–	109	28	–	–	–	–	274	274
Ringer's solution U.S.P	IV and subcutaneous	147	4	4	–	155	–	–	–	–	–	310	310
Dextrose* 5% in Ringer's solution	IV and subcutaneous†	147	4	4	–	155	–	–	–	50	252	310	562
Levugen* 5% with electrolyte No. 75	IV and subcutaneous†	40	35	–	–	40	20	15	–	50	277	150	419.5
Dextrose 5% in water	IV and subcutaneous†	–	–	–	–	–	–	–	–	50	252	–	252
Dextrose 5% in saline	IV and subcutaneous†	154	–	–	–	154	–	–	–	50	252	308	560
Dextrose 5% in 0.45% saline	IV and subcutaneous†	77	–	–	–	77	–	–	–	50	252	154	406
Dextrose 2½% in saline	IV and subcutaneous†	154	–	–	–	154	–	–	–	25	126	308	434
Levugen 2½% in 0.45% saline	IV and subcutaneous†	77	–	–	–	77	–	–	–	25	139	154	293
Dextrose 2½% in ½ Ringer's	IV and subcutaneous†	74	2	2	–	78	–	–	–	25	126	156	282

Dextrose 2½% in lactated Ringer's	IV and subcutaneous†	65	2	1.5	–	54.5	14	–	–	25	126	137	263
							(HCO_3)						
Levugen 5% with electrolyte No. 158	IV and subcutaneous†	140	10	5	3	103	55	–	–	50	277	316	592
Amigen‡ 3⅓%, dextrose 3⅓% in ⅓ lactated Ringer's	IV and subcutaneous†	63	11	1	–	50	9	16	260	33⅓	168	410	578
Amigen 5%, Levugen 10%	IV	30	15	–	–	22	–	23	390	100	554	480	1023
Amigen 5%, dextrose 5%	IV	30	15	–	–	22	–	23	390	50	252	480	721
Amigen 5%, dextrose 10%	IV	30	15	–	–	22	–	23	390	100	504	480	973
Levugen 10% in water	IV	–	–	–	–	–	–	–	–	100	554	–	554
Dextrose 10% in water	IV	–	–	–	–	–	–	–	–	100	504	–	504
									(NH_4)				
Levugen 10% with electrolyte No. 150	IV	63	17	–	–	150	–	–	70	100	554	300	854
Levugen 10% in saline	IV	154	–	–	–	154	–	–	–	100	554	308	862
Dextrose 10% in saline	IV	154	–	–	–	154	–	–	–	100	504	308	812

*Dextrose used is U.S.P. dextrose which contains one molecule of water of hydration for each molecule of dextrose. Therefore, 50 Gm. of U.S.P. dextrose supplies less dextrose than 50 Gm. of pure dextrose. The fructose used in Levugen solutions does not contain any water of hydration and 50 Gm. supplies a full 50 Gm. of fructose. Thus, a 5 per cent solution of dextrose contains only 252 milliosmols per liter and a 5 per cent solution of fructose contains 277 milliosmols per liter.

†Administer subcutaneously with caution.

‡This assumes that Amigen has an average molecular weight of 128 and that the amino acids and peptides are not ionized to any appreciable extent.

chemical-combining power of only 16 mEq. per liter. Sodium, with a weight of 326 mg. per 100 ml., has a chemical-combining power of 142 mEq. per liter. So protein is a locomotive, after a manner of speaking, and sodium an airplane!

The total plasma cations weigh only 356 mg. per 100 ml., but have the same chemical-combining power as the total plasma anions which weigh 6,948 mg. per 100 ml.

The milliequivalent represents the "horse-power rating" of a given electrolyte. It is defined as that amount of an element or ion which will combine with, or be equivalent in chemical-combining power to, 1/1000 of a gram atom of hydrogen.

MILLIEQUIVALENT COMPARED WITH MILLIOSMOL

In most instances the weight of a milliequivalent of a substance is the same as the weight of a milliosmol. Thus, a milliequivalent of all cations or anions having only one positive or negative electrical charge will contain the same number of particles as a milliosmol of any of those cations or anions. However, there are some cations and anions that have more than one electrical charge, such as calcium, magnesium, and the sulfate radical. These latter three have two electrical charges each. Therefore, a solution of each of them that contained enough particles as ions to exert an osmotic pressure of one milliosmol would contain enough electrical charges to be equivalent to 2/1,000 of a gram-atom of hydrogen, or, by definition, would contain 2 milliequivalents of the substance.

MILLIEQUIVALENTS AND MILLIOSMOLS IN TYPICAL SOLUTIONS

Table I is a list of the more frequently used parenteral solutions. The milliequivalents and milliosmols contained in each solution are also listed. A number of points should be noted.

1. Carbohydrates, because they are nonelectrolytes and do not have any electrical combining power, are not listed as contributing any milliequivalents to the solutions.
2. Carbohydrates in solution do exert osmotic pressure and do contribute to the total osmolarity of the solution.
3. A 5 per cent carbohydrate solution in water is approximately isotonic with blood plasma.
4. A 10 per cent carbohydrate solution in water has about twice the osmolarity as blood plasma and is, therefore, hypertonic in relation to the blood plasma.
5. Although the carbohydrate in the solutions causes the osmolarity of the solutions in many instances to be greater than that of plasma, no difficulty is usually encountered so far as upsetting the osmotic relationships in the body when the solutions are given intravenously. This is because the carbohydrate is removed from the blood quite rapidly and the solution itself is diluted by the total amount of blood and fluid in the body.

Table II, for the sake of comparison, indicates the respective milliequivalent and milliosmolar contents of the three major fluid types in the body, namely, extracellular fluid which is made up of the intravascular and interstitial fluids, and the intracellular fluid.

CLINICAL CONSIDERATIONS

The body regulatory mechanisms have two major functions in relationship to the substances dissolved in the body water. The first function concerns the maintenance of the proper chemical composition of the various types of body fluid (i.e., maintain proper levels of the sodium, potassium, etc., in the different types

TABLE II. MILLIEQUIVALENT AND MILLIOSMOL DISTRIBUTION AND CONTENT PER LITER OF FLUID

FLUID	ELECTROLYTES IN MILLIEQUIVALENTS/LITER										TOTAL MILLIEQUIVALENTS PER LITER	TOTAL MILLIOSMOLS PER LITER
	NA^+	K^+	CA^{++}	MG^{++}	CL^-	HCO_3^-	$HPO_4^=$	PROTEIN	$SO_4^=$	ORGANIC ACIDS		
Intravascular fluid* (blood plasma)	142	5	5	5	103	27	2	16	1	5	308	296.5
Interstitial fluid*	147	4	2.5	2	114	30	2	1	1	7.5	311	300.75
Intracellular fluid	35	115	5	27	25	10	80	47	20	–	364	305

*The intravascular and interstitial fluids make up the extracellular fluid.

of body fluids). The second function, which is the primary consideration of this paper, is related to the maintenance of the proper concentration of the dissolved substances in the various body fluids (i.e., maintain the total number of particles dissolved in the water of the different body fluids at the proper level and, thus, the proper osmolarity or tonicity of the fluids).

Consideration of several clinical examples may help in understanding these two functions. In diabetes mellitus, the blood dextrose rises to high levels if not properly controlled. These high levels of dextrose will increase the osmolarity or total concentration of dissolved substances in the body fluids.[2] In an attempt to lower the osmolarity of the fluids, the body will excrete large amounts of electrolytes, such as sodium, potassium, and chloride, as well as the dextrose, into the urine. This compensation for the hyperosmolarity of the body fluids caused by the dextrose will eventually produce a change in electrolyte concentration in the body fluids. Examination of the blood may reveal that the level of its electrolytes are lower than normal. A similar situation may occur if excessive amounts of carbohydrate-containing solutions are given continuously over a long period of time.

If an excessive amount of a solution such as normal saline is given, the kidney may not be able to excrete all of the sodium chloride as rapidly as it enters the body. This will result in an increase in the osmolarity of the extracellular fluid. The body will then be forced to retain water in order to achieve proper osmolarity of the extracellular fluid and edema may result.[3] A compositional change will also probably occur with a rise in extracellular chloride and a decrease in extracellular bicarbonate.

If an excessive amount of water is given, the osmolarity of the body fluids may be reduced to such an extent as to produce a water intoxication syndrome.[3] Numerous other examples could be given.

SUBCUTANEOUS ADMINISTRATION OF FLUIDS

A question that arises frequently in parenteral fluid therapy concerns the advisability of administering any particular solution subcutaneously. Infants and small children, adults with thrombosed veins, and patients in shock present a real problem when the intravenous route for parenteral therapy is attempted. Because of the great difficulty encountered in getting a needle into the veins of these patients, the doctor is tempted and frequently does give the parenteral fluids subcutaneously. Most of the time this causes the patient no harm, but there are very distinct and real dangers involved which should be kept in mind.[4]

There exists the danger of the occurrence of a shift of water and electrolyte from the extracellular fluid into the subcutaneous pool of fluid. This is particularly likely to occur when carbohydrate in water solutions are administered and to a lesser extent with carbohydrate in hypotonic electrolyte solutions.

As mentioned previously, the "semipermeable" membranes in the body not only permit the passage of water molecules, but also molecules of dissolved substances, such as fructose, glucose, and electrolytes. The body

membranes make use of this ability not only to maintain the osmolarity of the body fluids within fairly narrow limits, but also to keep the levels of the various dissolved substances within narrow limits.

Fluids given intravenously are introduced directly into the intravascular fluid. This permits the body homeostatic mechanisms immediate access to these fluids so that the proper adjustments can be made in order to maintain the proper osmolarity and electrolyte composition of the body fluids. Fluids given subcutaneously form a pool which must be absorbed into the intravascular and interstitial fluids. Before and during the process of their absorption, the body attempts to convert this subcutaneous pool into fluid that has the same approximate composition and concentration as the extracellular fluid.

Fluids administered subcutaneously that differ markedly in composition or concentration from the extracellular fluid will attract not only water but electrolytes. The amount of water and electrolyte that must be withdrawn from the extracellular fluid depends upon the amount of subcutaneous fluid administered and its difference in concentration and composition from the extracellular fluid. If an extracellular water and electrolyte deficit is created which is severe enough, peripheral vascular collapse will occur and the patient will go into shock. It becomes evident that the patients who are most in need of fluids and in whom the intravenous route presents the most difficulty are the ones who are most likely to be harmed by extensive subcutaneous fluid therapy.

It now becomes possible in the light of the preceding information to indicate which of the fluids in Table I may or may not be given subcutaneously and also to indicate which ones fall into a borderland between these two extremes. The latter may be given subcutaneously if adequate caution and the proper selection of patients are observed. It should be remembered that the solutions which are indicated as being satisfactory for subcutaneous administration may not provide the daily water and electrolyte requirements in proper proportions. Thus:

1. No 10 per cent carbohydrate-containing solution should ever be given subcutaneously.

2. Five per cent carbohydrate in water solutions should be given only with great caution, if at all, subcutaneously.

3. Two and one-half or 5 per cent carbohydrate in isotonic electrolyte solutions should be given with a moderate amount of caution, keeping in mind the fact that they have about twice the osmolarity of the extracellular fluid, and will attract a moderate amount of water and electrolytes from the extracellular fluid during the course of their absorption.

4. Two and one-half or 5 per cent carbohydrate in hypotonic electrolyte solutions can be given subcutaneously, but the paitent should be watched closely for any evidence of excessive loss of fluid or electrolyte from the extracellular fluid into the subcutaneous pool of fluid. This may be indicated by a rise in the pulse rate or fall in the blood pressure.

5. Isotonic electrolyte solutions can be given subcutaneously without the danger of withdrawal of water from

the extracellular fluid. However, if their electrolyte composition differs markedly from that of the extracellular fluid and if given in large enough amounts, they may produce undesirable and even dangerous changes in the extracellular fluid electrolyte composition.

6. Lactated Ringer's solution is the best-suited solution for subcutaneous use because it closely resembles the extracellular fluid in electrolyte composition and concentration.

SUMMARY

In this paper an attempt has been made to present a detailed yet simple discussion of the significance of tonicity in clinical medicine by:

1. Explaining osmosis.

2. Defining terms used in clinical medicine relative to tonicity.

3. Distinguishing between milliosmols and milliequivalents.

4. Presenting clinical examples of aberrations in body fluid tonicity.

5. Discussing the dangers inherent in the subcutaneous administration of fluids.

6. Indicating a recommended route of administration for various types of parenteral fluids.

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Physiologic Aspects of Pediatrics

THE PHYSIOLOGIC BASIS FOR THE USEFULNESS OF FRUCTOSE

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SHOULD fructose be used more extensively in pediatrics? It has received extensive trials in adults, but has been largely ignored by pediatricians. The sugar has several unusual properties which have been recognized for many years, but its key position in metabolism became known only recently and it now claims a place with glucose as a "physiologic" sugar.

THE SPECIAL ROLES OF FRUCTOSE

Cori and others[1, 2] have shown that fructose enters the glycolytic pathway as directly as glucose, but at a different site and under the control of a separate enzyme system (Fig. 1). It is first converted to fructose phosphate, which is an essential intermediate in glycolysis; and all glucose burned by glycolysis must be converted to this compound at one stage in its metabolism. Fructose is metabolized more rapidly than glucose. It does not circulate in any appreciable concentration in the blood of normal adults, perhaps because the extreme rapidity with which it is metabolized prevents any large accumulation in the blood; its rapid utilization permits parenteral administration without excessive hyperglycemia. Unlike glucose, its removal from the blood is apparently not insulin controlled, and it disappears from the blood of untreated diabetics at a normal rate.[3] Fructose appears to have some special significance to mammalian fetuses, which have appreciable levels of fructose in the blood. In the early human fetus, the ratio of fructose to glucose is 1:2.[4] The concentration in fetal lamb blood likewise is high early in gestation and gradually declines as term approaches. Its site of origin is probably the placenta,[5] which converts both maternal and fetal glucose into fructose; the fructose is secreted only into the fetal circulation, where it is partly metabolized and partly excreted by the fetal kidneys into the amniotic fluid. Its presence in amniotic fluid was first demonstrated just a century ago by Claude Bernard. Needham[4] suggested that fructosuria in the adult is an inborn error of metabolism representing the persistence of a fetal type of metabolism. The reason for a special provision of fructose for the fetus is unknown; perhaps the elaborate control mechanism for glucose was established later phylogenetically and merely superimposed on the more direct metabolic pathway for fructose. Sugar homeostasis in all vertebrates is effected with glucose, but at least one type of cell is maintained almost exclusively on fructose: the physiologic carbohydrate for spermatozoa is fructose,[6, 7] which is added to semen mainly by the seminal vesicles. These peculiarities of fructose suggest that it may have some advantages over glucose in certain clinical situations, the most obvious of which are diabetes and parenteral feeding.

FRUCTOSE AND DIABETES

The key position of fructose phosphate in glycolysis and its independence of insulin has again raised interest in the use of fructose for diabetics, who have long been known to be capable of metabolizing it at least to a limited extent without insulin. Sporadic trials have been made for over half a century, but without impressive clinical benefit. Winkowski[8] in 1890 was first to observe a protein-sparing action of fructose in diabetic dogs; Verzár[4] found that it raised the respiratory quotient of depancreatized dogs for a limited time, but after repeated use failed to do so. Fructose has had numerous trials in human diabetics; Joslin and associates[9] stated that it was apparently utilized for a few days, but that subsequently glycosuria recurred at its previous level. The ineffectiveness of fructose in the diabetic is probably due to its extensive conversion to glucose. Since the conversion occurs in the intestine[3, 10] as well as other organs, oral administration of fructose is particularly disadvantageous. The *diminishing* effectiveness reported by many observers is more difficult to explain. Deuel[11] suggested that conversion of fructose to glucose became more efficient as enzyme systems became adapted to heavier loads of fructose. Recent investigators,[12, 13] however, have failed to demonstrate diminishing effectiveness in diabetics. Many of the older observations indicating its transient utilization date from the preinsulin era, and it seems likely that the subjects upon whom the earlier observations were made were diabetics with depleted liver glycogen. One would expect that fructose was rapidly used initially to replenish these depleted stores; after this need was filled, apparent utilization diminished and a greater fraction

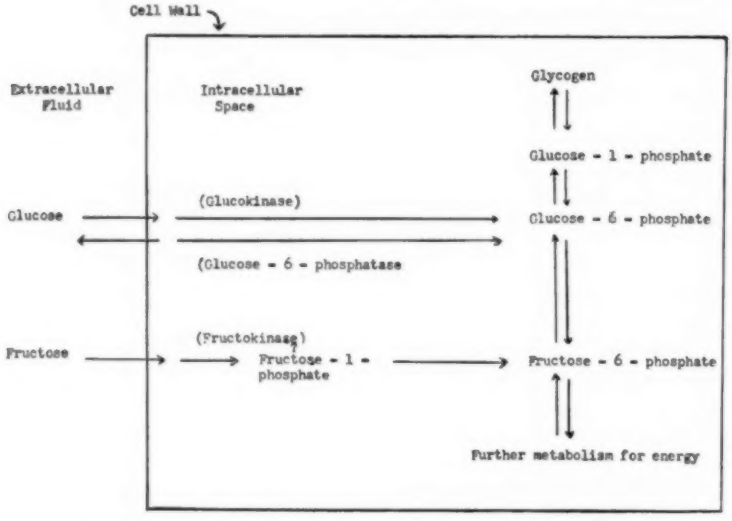

Fig. 1.—Early stages in glycolysis. The conversion of glucose to glucose-6-phosphate is insulin controlled, but the conversion of fructose to fructose-6-phosphate is not.

was converted to glucose and lost in the urine. A portion burned for energy probably continued to be utilized. This amount must be small, because many attempts to treat diabetic acidosis with fructose but without insulin have failed. The extensive conversion of fructose to glucose in the liver and intestines is the main obstacle to its usefulness in diabetes. Clinical benefits from its use can be attributed to the small fraction metabolized for energy, but the need for insulin remains in order to metabolize the large fraction converted to glucose, and no superiority over the usual forms of management has been established.

FRUCTOSE FOR PARENTERAL FEEDING

Fructose should have real advantages for parenteral feeding in nondiabetic patients. Fructose disappears from the blood more rapidly than glucose[14] and, hence, more calories can be supplied with less urinary loss of water and electrolytes than for equivalent amounts of glucose. Urinary losses are usually reported to be lower in spite of the fact that fructose is probably a nonthreshold substance and is spilled to some extent even at low blood levels. Weichselbaum and others[15] found in normal adults that the urinary loss of fructose was less than 6 per cent of the administered dose (100 grams at 0.6 to 2.0 Gm. per kilogram per hour in 10 per cent solution) compared with a 25 per cent loss after glucose given at equivalent rates. The findings of other observers[14, 16] were similar, though Miller and others[3] found at lower infusion rates that as much fructose was lost as glucose. The discrepancy probably reflected the loss of some fructose at low blood levels where little or no glucose was lost; an advantage of fructose over glucose becomes apparent at higher infusion rates, where the rapid removal of fructose prevents high blood levels and large urinary losses such as are found after rapid infusion of glucose.

Fructose is readily metabolized in the intact animal; its administration to normal subjects was followed by a rapid rise in the respiratory quotient,[17] blood pyruvate,[18] blood glucose,[3, 15] hepatic glycogen,[19] and carbon dioxide excretion. The respiratory quotient and hepatic glycogen rose more rapidly than after glucose, and the elevation in blood pyruvate was three times greater[3]; fructose was more effective than glucose in sparing protein.[20] The rapid utilization of fructose is its main advantage in parenteral feeding but also presents a potential hazard. Weichselbaum and others[18] found that fructose infused during anesthesia at high rates (3 Gm. per kilogram per hour) produced a rise in blood pyruvic acid sufficient to cause a significant acidosis. Infusion at the same rate on normal, unanesthetized individuals caused no appreciable change in acid-base balance, and lower infusion rates caused no difficulty in either anesthetized or normal individuals. Acidosis did not impair fructose utilization in dogs.[21]

USE OF FRUCTOSE IN INFANTS AND CHILDREN

Fructose has not been used extensively in pediatrics, and no published reports of its parenteral use in infants or children have appeared. Its presence in fetal blood and absence from adult blood suggests that young infants may metabolize the sugar somewhat differently than older children or adults, and specific information is

needed. The most advantageous use of fructose should be in those infants and children who must be maintained largely or entirely by parenteral feeding. Certain surgical patients and infants with severe diarrhea and vomiting are the most likely candidates. Successful prolonged total parenteral feeding has not yet been achieved, largely because of deficient protein synthesis. Fructose is effective in sparing protein, but its combination with amino acids for parenteral use does not resolve the problem, presumably because other factors essential for protein synthesis are not supplied. Nevertheless, the substitution of fructose for glucose should make the problem of short-term maintenance easier. Over periods of a few days the problem is mainly one of supplying sufficient calories, and faster utilization of fructose permits administration of larger quantities with lower urinary losses of water, electrolytes, and sugar. Administration of fructose should probably be at rates below 3 Gm. per kilogram per hour; the use of 10 per cent solutions reduces the necessary fluid volume. Reports on infants and children of acid-base balance and on urinary loss of water, sugar, and electrolytes would be value. If these follow the patterns found in adults, fructose should have a definite advantage in the parenteral feeding of infants and children and should receive more extensive trial.

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Psychologic Aspects of Pediatrics

THE MEASUREMENT OF INTELLIGENCE IN CHILDREN WITH CEREBRAL PALSY: THE COLUMBIA MENTAL MATURITY SCALE

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THE degree to which the multiple handicap of the child with cerebral palsy interferes with performance of standard tests has received much comment. However, there are a number of other aspects involved in the mental measurement of the cerebral palsied child which are not commonly considered.

The child with cerebral palsy is handicapped not only in the obvious factors of speech, manipulation, and locomotion, but he is also often severely limited in the social experiences common to the average child. Most of the intelligence tests in common use today have been standardized upon a population having fairly homogeneous background of interaction with their environment. The normal child is in daily contact with all the multitudinous cultural artifacts and social patterns which contribute to the structures of modern community living. The average preschool child has daily experiences with balls, hoops, knives, forks, cats, dogs, toy cars, and with other little boys and girls who run, jump, laugh, cry, talk, sing, fight, fall, boast, tease, get spanked, and often imitate their mothers, fathers, and favorite fictional heroes. Thus, by the age of 5 or 6, they are "world wise" and keenly aware of the meanings of the things about them.

In sharp contrast to the normal child, let us consider the child who is severely handicapped by cerebral palsy. Assuming that such a child has not learned to walk by his fifth year, has little or no intelligible speech, and is unable to manipulate objects in the normal manner, it follows that the environmental experiences which he has had will not be comparable to those of the average child of his age. Not being able to walk, he has probably spent a much greater portion of his time within the confines of the house or yard than has the average child. His difficulties in speech have probably barred him from group play, and thus he has not shared the life experiences common to his age group. Therefore, since many of the items in most intelligence tests are based upon the daily life experiences of the average child, many severely handicapped cerebral palsied children may do poorly on such a test, regardless of their potential ability.

The depressing effect of environmental deprivation upon I.Q. scores is a long-accepted psychological fact which applies not only to the mental

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evaluation of cerebral palsied children, but as a general factor in the field of mental testing. Freeman[5] studied a group of 401 children placed in foster homes of higher socioeconomic level than their original homes, and showed that these children gained an average of ten I.Q. points in a four-year period. In addition to Freeman's study, numerous other authors[9] have demonstrated a definite relationship between environmental deprivation and low scores on standard intelligence tests.

A second factor that requires consideration in the evaluation of the cerebral palsied child is the emotionally toned reaction pattern often found in these children. This pattern is similar to a portion of the syndrome of "childhood aphasia." In cerebral palsied children who do not show the aphasic signs of perseveration, defects in abstraction and categorization, temporal and spatial rigidities, clear-cut agnosia and apraxia, and persistent vasomotor anomalies, "aphasic reactions" are often seen in terms of propositional defects, catastrophic reaction, hyperirritable attention, emotional lability, and initiatory confusion and delay. This reaction pattern often detracts considerably from the test performance of the child with cerebral palsy.

Phelps[8] believes that the emotionally toned reaction pattern is mainly associated with athetosis. While this seems essentially true, our experience suggests it is found in varying degrees in most cases of cerebral palsy.

The propositional factors in the behavior of children with cerebral palsy are well known to all who work within this field. The behavior of the cerebral palsied child who is able to lift a full glass of water without spilling any, and yet is unable to lift a warm glass of milk, is a common observation to most workers who have observed the routine habits of these children. Propositional variations are seen in other areas of behavior. The cerebral palsied child who can talk quite plainly to his pet dog or cat but whose speech becomes unintelligible when speaking to his parents or teachers is demonstrating defective propositionality. The athetotic child who is relatively free from tremor when he is alone but who has a great increase of involuntary movement when he is with a group of people is also showing a propositional aberration. Propositional stress is essentially a condition of specific emotional pressure. When situational pressures bear directly upon areas of behavior which have emotional importance to the child, these areas of behavior are adversely affected. This is by no means an "abnormal" type of reaction. Consider, for instance, the typist who makes errors in typing when her employer is watching her, or the adroit conversationalist who blocks and fumbles his words when speaking before a large audience. In the cerebral palsied child, whose speech, movements, and general appearance have consistently elicited unfavorable social reactions, propositional factors have a greater effect on overt behavior than they do on the average person. In the psychometric testing situation, the child's recognition of the fact that he is being "tested" is often enough to raise the propositionality of the situation to such a degree that he is unable to do things which he can do with ease in other situations.

Closely associated with propositionality are emotional lability and catastrophic reactions. A catastrophic reaction is usually a response to failure or imminent danger of failure. To the child who has experienced failure consistently and who probably has been directly or indirectly criticized for his failures, failure or the danger of failure creates severe emotional stress and often leads to catastrophic reactions. While there are many varieties of catastrophic reactions, they are essentially of two basic types: The child may withdraw from the situation by simply sitting quietly and doing nothing or "blanking out"; or he may give an apparently aberrant response simply as an attempt to "do anything" to get out of his difficulty. This latter type of catastrophic situation is the basis for many of the "wrong answers" given by the cerebral palsied child in intelligence tests. For example, in response to the Binet Picture Vocabulary, a child with a severe speech defect may say "knife" instead of "scissors" simply because it is easier to say "knife" at the moment. Or, again, a child may simply stare blankly ahead and say nothing in response to a verbal comprehension question, not because he did not know the answer, but because emotional pressures are too great to permit him to speak at the moment. Catastrophic reactions can generally be avoided or considerably diminished by eliminating the obvious "test" aspects of the situation. If the catastrophic reaction occurs, situational rapport can often be re-established by back-tracking to an item with which the child had success earlier in the test.

In addition to the factors already mentioned, the problems of mental evaluation in cerebral palsy is further confounded by perceptual defects. The term "perceptual defects" is here being used in reference to aberrations of sensory intake, and does not refer to defects of the apperceptive or cognitive type. The most common perceptual defects within our experience in the testing of cerebral palsied children are figure-ground reversals, confusion in spatial orientation, and specific distortions in form perception. The latter is consistently seen in the children's performances with such items as the Seguin and Binet Formboards. The child who is consistently able to adapt the star, the half-circle, and the cross, but who consistently confuses the square, the diamond, and the rhomboid is probably giving evidence of defective perception rather than an inability to make proper associations.

The foregoing discussion gives some indication of the types of problems which must be considered in the mental evaluation of children with cerebral palsy. The total picture, however, is even more complex. Various studies have attempted to isolate the general psychological characteristics of children with brain injuries. While differing lists of "clinical signs of brain injury" have been compiled by various workers,[2, 7] there seems to be general agreement that the following behavioral characteristics are commonly observed in cases of childhood brain injury:

1. *Deviant propositionality:* Under an optimal degree of situational pressure, the child fails at tasks (speech, motor, general communicative) which he is able to do with relative ease when the situational structure is less threatening to his emotional security.

2. *Perseveration:* Under propositional stress, the child has a tendency to repeat a previously rewarded response, rather than to make an adequate response to the next of a series of communicative interactions.

3. *Catastrophic reactions:* As situational pressure mounts, the child with a brain injury tends to make aberrant psychic and/or psychomotor responses; crying, withdrawal from the situation, temper outbursts, vomiting, etc.

4. *Deviant patterns of abstraction and categorization:* In problem-solving situations, the child may attack the problem on the basis of factors not commonly recognized as prime situational determinants. For example, when asked to match groups of colored yarns, matching may be done on the basis of color intensity, or saturation, rather than hue.

5. *General rigidities:* A child displaying general rigidities often has difficulty in accepting new situations, or minor changes in familiar situations. He is often disturbed by minor alterations in the temporal and spatial organization of his environment; and may react unfavorably to disorderly spatial arrangements.

6. *Hyperirritable attention:* Brain-injured children often have difficulty in selecting one stimulus complex out of a broad field of stimuli. In a testing situation, attentional "set" is easily disrupted by extraneous field stimuli.

7. *Emotional lability:* A child displaying emotional lability tends to overreact to the emotional components of a situation. He laughs, cries, and becomes angry quite readily. His emotional reactions are subject to rapid alterations. At times his reaction may be entirely inappropriate to a specific situation.

8. *Initiatory delay and confusion:* Brain-injured children often have difficulty in initiating responses. Even when they "know the answer," they often require an inordinately long time to organize an appropriate response.

9. *Aprazias:* Some children with brain injury have difficulty performing at a high propositional level motor acts which are well within their basic physical limits.

10. *Perceptual defects:* Many children with brain injury show aberration in intake and interpretation of visual, auditory, and general kinesthetic-proprioceptive-haptic stimuli.

11. *Vasomotor lability:* Vasomotor lability is a catastrophic sign consisting of excessive perspiration, flushing, pallor, etc.

12. *Autistic behaviors:* Under situations of extreme situational stress, a child with a brain injury may "withdraw" in terms of the initiation of purposeless, nonadaptive activities; singing to self, rocking back and forth on chair, twisting head from side to side, etc.

It must be noted here that all of the above "signs" are most likely to be manifested when the child is put into a "test" situation, a situation which threatens his emotional security.

It is thus apparent that brain-injured children have certain psychological characteristics which, by their functional and operational features, must be carefully considered in test design, and in the total performance complexes elicited from such children by psychological testing procedures. This problem, that of the effect of catastrophic reactions, perceptual defects, categorical difficulties, etc., on intelligence test scores, has received considerable attention in the recent literature[1, 7] and needs no further discussion at this time.

Within recent months, the Columbia Mental Maturity Scale has gained some popularity as an instrument for the evaluation of the intelligence of children with cerebral palsy. Its authors, Drs. Burgemeister, Blum, and Lorge, report that this test is ideally suited to this purpose because it demands no verbal response, a mini-

mum of motor response, and little verbal communication between administrator and subject.

The test is composed of 100 items, each printed on a card 6 by 19 inches. Each item consists of a series of from three to five drawings of things which would have some degree of familiarity even to severely disabled children with markedly limited backgrounds of environmental interaction. In all items, the task asked of the subject is to point to one drawing in the series which is different from, or unrelated to, the others in the same series. The cards are arranged in order of increasing difficulty, the bases of selection ranging from gross differentiation of form or color, to recognition of more abstract functional and generic classifications. The mental age range of the test is from 3 to 12 years.[3]

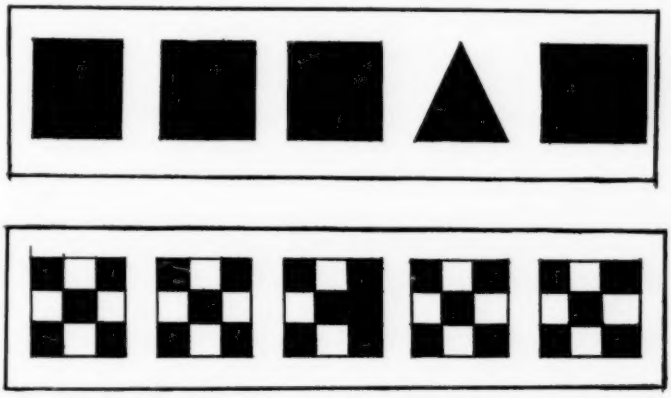

Fig. 1.—Two of the cards from the Columbia Mental Maturity Scale. In each item, the child being tested is instructed: "Point to the one that does not belong with the others." The lower card has proved to be very difficult for children with visual-perceptual difficulties.

The authors state that the Columbia Mental Maturity Scale was conceived to overcome the oft-noted difficulties involved in obtaining accurate evaluations of the intelligence of children who have severe speech and motor impairments arising from cerebral palsy and similar handicapping conditions. From the description of the test, it would seem that it is well suited to this end.[3] The purpose of this investigation, conducted at the Institute of Logopedics, an habilitation clinic serving individuals with speech and communication problems arising from brain injuries and numerous other causes, was to determine whether the Scale might be adopted as part of the standard psychological screening procedures, especially in reference to children with brain damage.

For purposes of primary orientation, the Columbia Mental Maturity Scale was first administered to thirty non-brain-injured children who were attending the clinic for correction of minor speech difficulties. These children, fifteen males and fifteen females, ranged in age from 5.25 to 11.5 years, with a mean C.A. of 8.75 years. All of these children had within recent months been administered Form L of the Revised Stanford-Binet. The group showed a mean Stanford-Binet I.Q. of 97.8. The Columbia Mental Maturity Scale yielded a mean M.A.

8.65 years, and a mean I.Q. of 98.8. A Pearson correlation run between the Stanford and the Columbia I.Q. scores yielded a coefficient of r = .82. These findings are in essential agreement with the validity data presented by Burgemeister, Blum, and Lorge.

The Columbia Mental Maturity Scale was next administered to thirty children with cerebral palsy. These children, eighteen males and twelve females, all had speech and motor impairments of various degrees of severity; but, when approached with special recognition of the factors involved in the mental evaluation of brain-injured children,[2] were able to make adequate responses to administration of the Stanford-Binet. The children in this group ranged in age from 5.5 to 12.5 years, with a mean C.A. of 9.10 years. The mean Binet M.A. was 6.18 years, giving a mean I.Q. of 67.9. Administration of the Columbia Mental Maturity Scale to this group yielded a mean M.A. of 4.80 years, and a mean I.Q. of 52.9. The Stanford-Binet and Columbia I.Q. scores correlated at r = .61.

Thus there was a marked discrepancy between scores made by brain-injured children on the Stanford-Binet and the Columbia Mental Maturity Scale, the Columbia test yielding the *lower* mean score. In two cases the discrepancy was 25 I.Q. points. Seven children scored 15 to 24 I.Q. points lower on the Columbia than on the Stanford-Binet. Twelve scored 5 to 14 points lower. Six scored 1 to 4 points lower; and three obtained Columbia scores 1, 3, and 4 I.Q. points above their respective Binet scores. From these data arose the question of the possible reasons for this rather startling discrepancy in scores. What factors, either in the children, or in the design of the test, or in both, could be responsible for the observed deviations?

Scrutiny of the test items suggested that the intellectual functions heavily stressed in the Columbia Mental Maturity Scale are visual perception, categorization, and abstraction. All these factors are commonly impaired in children with brain injuries. It must be stressed here that children with cerebral palsy have brain injuries which give rise not only to locomotor and motor speech impairments, but also often to impairments in general language and communicative functions.

It has already been stated that the Columbia Mental Maturity Scale puts heavy stress upon visual perception, and abstraction and categorization. In a study now in process at the Institute of Logopedics, out of 100 cerebral palsy cases, 62 per cent have abstracting and categorizing difficulties, while 44 per cent show marked deviations in visual perception. The perceptual defects are of several varieties including poor recognition of gross form differences, figure-ground reversals, and poor isolation of minor details. All factors are heavily weighted in the Columbia Scale.[2]

Analysis of the performances of the thirty brain-injured children tested with the Columbia Scale indicated that many responses were contaminated by deviant abstraction and categorization, and by perseveration. The first item in the Scale presents two small red squares and one large blue circle. The child is expected to point to the blue circle in response to the examiner's request, "Point to the picture that does not belong with the

others." If the child fails to do so, he is shown that the big blue circle is different from the little red squares, and therefore "does not belong." Eighteen of the thirty brain-injured children in this study did not readily comprehend the meaning of "does not belong," and needed further demonstration of the task with the next two cards; two blue squares and a red circle of approximately the same size; and two large yellow squares and a small red square. Of the eighteen children failing to comprehend the task on the first card, fifteen chose one of the blue squares as the response for card 2. Investigations of these responses indicated *perseveration* of a spatial response in four cases; i.e., the blue circle on the first item was to the child's right-hand side of the card, and the child pointed to the blue square at the right of card 2. The remaining eleven children gave evidence of *deviant patterns of abstraction and categorization.* Each chose one of the blue squares as the second response; and when questioned regarding their responses, replied to the general effect that "it was *blue*, like the circle, so it doesn't belong."

Nine children chose one of the two larger yellow squares as the response for card 3, because it was "*big*, like the big ball" (on the first card).

It is evident that the items on the first three cards of the Columbia Mental Maturity Scale are so arranged as to be confusing to children with brain injuries, giving rise to abstracting and categorizing difficulties. Such children may respond either to position, color, size, or shape. It was also noted that some children in this group tend to react to their own confusion by perseverating the first response.

It is not the intent of this paper to analyze in terms of the brain-injured syndrome the possible faults of each item in the Columbia Mental Maturity Scale. It may be well, however, to illustrate a few which gave the most difficulty to the brain-injured children used in this study. The first three cards have already been discussed. Card 5 presents two red triangles and a yellow rectangle. Card 6 presents two yellow half-circles and a red triangle, leading to a tendency of color perseveration and categorical confusion on card 6. Card 22 shows two blue houses and a blue alphabet block, the detail of all items represented as white spaces in the blue matrix. This type of item is particularly susceptible to figure-ground visual perceptual disturbances. Card 35 shows five rabbits, four with upright ears and one with "floppy" ears, calling for good perceptual isolation of small detail. Card 37 presents a similar problem, as does card 39. Many of the cards above 39 present problems demanding high-order abstractions and excellent perceptual discrimination; and in some items a combination of both, factors in which many brain-injured children are markedly deficient.

Analysis of the results yielded by the children with cerebral palsy tested with the Columbia Mental Maturity Scale showed that nine children out of the thirty made scores which were in close agreement with their Stanford-Binet I.Q. scores, i.e., –4 to +4 points. Review of the psychological data previously gathered on these children indicated that in each of these nine cases there were no signs of brain injury other than the obvious motor and motor speech defects, four

cases with emotional lability, and two cases with initiatory confusion and delay.

Of the twenty-one children showing marked discrepancies between Stanford-Binet and Columbia Mental Maturity I.Q. scores, nineteen showed deviant patterns of abstraction and categorization. Fourteen showed marked defects in visual perception. Eleven had low catastrophic levels. Ten demonstrated marked initatory delay and confusion. Five demonstrated various types of psychological rigidity; and four had marked perseverative tendencies. Ten of these nineteen cases demonstrated combinations of two or more of the foregoing signs of high brain injury.

SUMMARY AND CONCLUSIONS

This paper has discussed some of the psychological problems presented by children with brain injuries which necessitate extreme caution in the evaluation of the intelligence of such children through the use of standard psychometric tests and interpretative orientations. It has also reported the results of a study of the effects of the discussed psychological factors upon the validity of the use of the Columbia Mental Maturity Scale as a measure of intelligence for children with brain injury. It is concluded that the results of this test, like any other standard test, must be accepted with reservation, and with careful consideration and complete recognition of the portion of the "brain-injured syndrome" presented by each child tested, inasmuch as current studies are suggesting that 60 to 70 per cent of all children with cerebral palsy examined at the Institute of Logopedics present two or more of the psychological signs of brain injury discussed in this paper.

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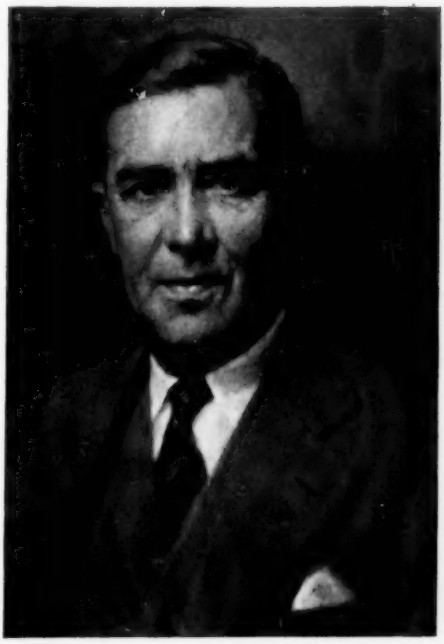
Pediatric Profiles

Kenneth D. Blackfan

(1883-1941)

IF EVER a man's life could be considered dedicated intensely to a single purpose, Kenneth Blackfan's was devoted to pediatric education. This attempt at a picture of Dr. Blackfan's life is written from the necessarily prejudiced point of view of one who was his student for eleven years at the Children's Hospital in Boston and whose memories of him are limited to the last fifteen years of his life which, almost certainly, he would have considered the most important period of his service to medical education. As I saw him, the dominant purpose during those years of his life was a persistent, almost ruthless, concern to develop an ideal teaching machine for pediatric education. His concept of the best type of pediatric education, if expressed today, would be considered entirely modern and would differ little from those who consider themselves now most progressive in this field. In essence, it consisted in a firm belief that one learned to be a good children's doctor only by "doing" pediatrics, not by being talked to, that one could not be a rounded physician without a real interest in progress of medical knowledge and some participation in research, and that a physician must place the well-being of each individual patient before all else, including the demands of teaching and research.



From an oil painting by Alexander James.

Dr. Blackfan's progress to his final position of a national figure in medical education and of chairman of the pediatrics department at Harvard was by no means an easy one. Some of the steps that he went through to gain experience, as well as a reputation, seem painful, and some might seem missteps. He probably spent as long a time in intense and financially unremunerative activity in the preparation of himself to be one of our great teachers as anyone in this country.

His early education did not indicate that his ultimate professional career would be in education and research. He was born in Cambridge, New York,

in 1883, and received his medical degree from near-by Albany Medical College in 1905 at the early age of 22 years. Probably no more important influence in his life arose than the coming to Albany of Dr. Richard Pierce as professor of pathology and bacteriology in Blackfan's Junior year. The interest of Dr. Pierce in the scientific aspects of medicine was very stimulating and it seems clear that the contact with this teacher was to make him ultimately dissatisfied with general practice. It is interesting to note how early some interest in the laboratory occupied him. He served briefly, but apparently most profitably, before and after his graduation as pathologist at the Albany Hospital and as assistant bacteriologist in the medical school there under Dr. Pierce. He then entered general practice with his father in Cambridge, New York. It was soon obvious that he was not contented with general practice and, as he developed a particular interest in children's work, after four years he went back to Albany with Dr. Harry Shaw. Still he was not contented, and in 1910 he went to Philadelphia to assist Dr. Sam Hammill.

After a few months he became a resident at St. Vincent's Foundling Hospital in Philadelphia under Dr. Hammill. This experience, as well as that in general practice, although not satisfying to him, nevertheless was worth while, and later on in his life he often referred to experiences that had been valuable to him there.

The St. Vincent's Foundling Hospital in Philadelphia must have been a shocking place for him to work. It is said that there was an infant mortality of some 90 per cent of those under one year. He and Hammill made some attempts at research there, studying the Calmet eye test and the von Pirquet skin test for tuberculosis. Soon, however, he was on the move again, and in 1910 he and Borden Veeder went to St. Louis, under that great teacher, Dr. John Howland, to help develop a pediatrics department in Washington University. This step was to prove a decisive one in his life, as his long association with Howland was to be a dominant influence on his whole career as was the case with others who became great teachers of pediatrics. Accordingly, when Dr. Howland left and was offered the professorship of pediatrics at Johns Hopkins and asked Kenneth Blackfan to go with him, he left his unfinished work and his close friend, Borden Veeder, and started his long experience at Johns Hopkins in 1912. Veeder has said, far too modestly, that perhaps his greatest contribution to scientific pediatrics was to stay in St. Louis and permit Blackfan to go with Howland. Blackfan spent eight fruitful years at Johns Hopkins as resident and as a teacher, finally obtaining the title of Associate Professor of Pediatrics. This period was the richest of his educational experience, and in spite of working for a pittance, he was happy there. After eight years he accepted the Chair of Pediatrics at the University of Cincinnati and three years later, in spite of the knowledge that a great opportunity was being offered by the expectation of a large bequest to his department, he accepted the professorship at Harvard University.

Dr. Blackfan had had difficulties at Cincinnati in establishing an independent department with full-time workers, but it is clear that his successor had an easier time because of

the work he had done. In a similar way, Blackfan had an easier time at Harvard because of the work of his immediate predecessor, Oscar Schloss, who had initiated the modernization of pediatric teaching there as Blackfan had at Cincinnati.

A picture of Dr. Blackfan's life must most importantly contain some discussion of the philosophy of teaching to which he doggedly devoted himself; a practical plan of teaching that would make possible the integration of hospital service with very great clinical responsibilities, with a department of a medical school primarily concerned with education and research.

He felt that the most effective way of teaching pediatrics at any level, undergraduate or graduate, was to allow the personal experience of the student by responsible contact with a patient, to motivate the student's study. Accordingly, as much as possible, students worked as junior interns, taking histories, doing physical examinations, and deciding what treatment should be carried out, and following up their own patients with recorded observations. This was, of course, not a new concept of teaching medicine except in the way he applied it, and the intensity of his desire to reach this end. Almost all clinical teaching, except for a relatively few lectures, was built around bedside or outpatient experience.

Kenneth Blackfan's primary interest undoubtedly was in the undergraduate medical student, and his feeling of responsibility there was extremely great. This devoted attitude toward teaching medical students was so apparent that sometimes his residents felt treated unfairly. It has been said, almost as a joke, that any medical student could get to see him and spend time with him with far greater ease than one of his residents. This was almost literally true. His contact with students was, nevertheless, reserved. He was no teacher acting like a "buddy." There was little joking with the students, but if it came to a dispute as to the amount of routine work a student should do in a clinical laboratory as compared with the house officer, there was no question about what his attitude would be. The student's job was to learn, not to help the resident. If the laboratory work was instructive, then he was willing to let the student do it, but he would not allow house officers to burden the student with routine work if he could help it when the resident could do the work just as profitably from the point of view of the student's education. An instructor did not get great sympathy for his complaints that a group of students was particularly poor or lazy. Blackfan's usual reaction was that the teaching must be wrong and not made interesting enough. A poor student first suggested to him a poor instructor.

Ward rounds with the students were relatively formal. They were actually not ward rounds in the traditional sense, although he would very often wander around the wards for a few minutes. Every ward round was prepared. He knew ahead of time which patients he was going to study and the hour would be directed, for the most part, toward the analysis of the clinical problems of two or sometimes three patients. The organization of the students' time he accepted as his responsibility. Others might work out the details for him but there was no sched-

ule that he was not thoroughly acquainted with and with which he would not interfere.

With the resident staff he was critical, and, as with the students, rarely informal, except with those who had been around him for some time. His ward rounds with the students or with the residents were always quiet and reserved, and strict discipline was maintained. He had developed a fine technique of reprimanding the resident staff, and so maintaining control, without ever raising his voice or using direct criticism. When a patient in his opinion was mishandled, a few remarks, perhaps to the students, made it clear to everybody where the fault lay, and that it was not with the students. He had an excellent memory, and a quiet word, almost casually dropped during ward rounds to the resident in charge, regarding something that ought to be done or something that should be looked up, was rarely forgotten. He might suggest that it would be worth while for Dr. X to look up the data on the incidence of a characteristic spinal fluid in mumps meningitis. Nothing more would be said about it perhaps for several weeks, and then quite suddenly Dr. X would realize that he was being publicly questioned about this matter with the full expectation that he would come up with a clear-cut answer as the results of his own investigation. If he did not, the quiet pause after his acknowledgment of ignorance and Dr. Blackfan's request for someone else to do the work were far more effective than any direct criticism could have been.

A very important feature of Blackfan's philosophy about training at the graduate level was his desire to integrate clinical and laboratory work. He was very pleased with the program which he developed at the Children's Hospital of having one or two men spend an extra year or so in the laboratories, usually before they came to their clinical work. These men got very valuable clinical experience and were expected to know a great deal about the patients while assigned to the laboratory. Many of them since have become outstandingly useful people in pediatric teaching because of this combined clinical and bacteriological or biochemical training.

Dr. Blackfan's relationship with his small patients was one of deepest interest and affection, but reserved and undemonstrative. Children never ran to him to be picked up, but, nevertheless, his calm and gentle handling of them, with the avoidance of any sudden motions or signs of impatience, enabled him to carry out his physical examinations with conspicuously more success than many of the resident staff could obtain. Although he would teach how a crying child could be examined, it was obvious that he did not feel satisfied himself with such techniques and took time to quiet the baby, or reassure the child, first.

There was no question but that every man who studied under him had the feeling that interest in the patient came first, second, and beyond anything else. No child's interest was expected to be sacrificed to the demands of teaching and research, or to hospital routines, rules, or customs. There were certain stories that he would tell repeatedly to illustrate his attitude that the patient's good must come first. I heard a story many times about the patient with meningococcic meningitis that he had treated in the outpatient

department of the Harriet Lane Hospital. A diagnosis of meningitis was made in the admitting room. Hospitalization was refused by an ignorant and belligerent parent, but, nevertheless, the father was persuaded to bring the child back repeatedly for care. He described how lumbar punctures were done daily, or twice daily, and antimeningococcic serum was administered intrathecally in the outpatient department in a manner that apparently was quite contrary to the general habits of that institution, and would be now. He boasted to us how this child was completely cured of meningococcic meningitis without ever being admitted to the hospital and used this as an illustration of the limits to which anyone must go in caring for children and to emphasize that no child should be punished for the ignorance or lack of cooperation of the parents.

He disliked discharging children "against advice." At that time, at least, a discharge "against advice" was a technicality that meant that the parents could not bring the child back for further care and that the hospital righteously washed its hands of him. When Blackfan was aware that this technique had been followed, he would be very critical indeed of all the circumstances. Usually the child was allowed to come back for care anyway. He always objected to the use of the word "case" in reference to a patient. The child's name should be used. He should be considered, not a 6-year-old male, a case of pneumonia, but as Johnny Somebody, 6 years old, who had pneumonia.

Blackfan was intensely interested in the establishment of the Academy of Pediatrics and, particularly, the Board of Pediatrics. There were differences of opinion among us at that time about this venture, it being felt by some (among them myself) that it was a step toward "trade unionism," or the guild system, with the basic idea of restricting the practice of pediatrics. Blackfan felt differently and his opinion has been thoroughly supported by time. Probably there is no organization where new memberships are welcomed more than in pediatrics, both in the Academy or in actual practice.

Blackfan was not a fluent speaker or writer. He was indeed a painful writer and it was painful to work with him, sitting by his desk at his request, when he tried to write something or when one presented him with an article, already written, for his criticism. Over and over, sentence by sentence would be pulled apart, reconstructed, moved around, sometimes ending just where it started. This plodding but thorough type of writing was one of the major reasons, I believe, why the loose-leaf system of Brennemann's *Pediatrics* was not the "Brennemann and Blackfan System." At first he was going to be a co-editor, but I believe he felt that Dr. Brennemann was going too fast and accepting articles too freely. In any case, he withdrew fairly early from this association. He did spend a great deal of time to help with several chapters, nevertheless, but his thinking with his pen was not fast enough, and his desire for perfection too great for him to work easily with others. He constantly emphasized very sound principles of scientific writing. He made the point repeatedly that a paper should make only one or two points, and those very clearly, and, as we have said, to bring this about with clarity and simplicity,

he would rewrite a sentence or a paragraph many times to the point of exhaustion by all those associated with him.

There can be little question as to the order of importance to him of the various components of his work. First and foremost, at all times and at all costs, came the patient's good, regardless of the parents' cooperation or possible demands of scientific curiosity. Next came the good of the medical students for whom he had a very great feeling of personal responsibility, although there was little personal intimacy with them. Next would surely come his graduate students. But over it all came the dedication to the perfection of his department as a working organization, clearly in the understanding that only through such a good working department could the other ends be properly met.

All this should not indicate that Blackfan had little interest in a personal life outside his work. Although he devoted many years as a bachelor to his postgraduate training, at first moving almost restlessly from one job to another, as we saw him at Harvard he was the picture of a contended family man. He was married to Mrs. Lulie Henry Bridges of Louisville, Kentucky, in 1920, when he was 37 years old, fifteen years after he received his medical degree. This was the year that he left Johns Hopkins University and, for the first time, had an independent position, and presumably his first income that could be called something more than a nominal sustenance salary. Mrs. Blackfan had previously been married and her son became as much of a son to Kenneth Blackfan as any child could be, and he was deeply involved in this boy's development and future. He had no children of his own. His marriage at 37 years of age did not cause him to deviate in any way from his main purposes, but must have made him immensely happier. One of the greatest pleasures of his life was the construction of a new home in Brookline which he and his wife planned in great detail themselves. Only those working closely with him could realize what intense pleasure its planning, its construction, and finally his life in it meant to him. Mrs. Blackfan was a beautiful homemaker and hostess, and their final home was perfect in all the little details of Southern graciousness that she could so well accomplish. Their summer home in Cambridge was also of great interest to the Blackfans. With the ill health which handicapped him, Kenneth Blackfan took a long summer period away from school, and during this time he caught up on his thinking, reading, and writing, and also occupied himself physically with the construction of this summer home. He started with a single cottage and then built up on the shore of a little lake a small number of guest houses, complete in themselves, so that he could have a tiny colony of his friends around him at various times during the summer months.

Blackfan was a member of the American Pediatric Society of which he became President in 1938, the American Society for Clinical Investigation, the American Institute of Nutrition, and the Association of American Physicians. He was an honorary member of the Philadelphia Pediatric Society and the Society for Pediatric Research.

He was greatly interested in a variety of research projects in biochemistry, nutrition, and hematology and his bibliography shows a great range

of interests. Almost all his papers were reports of studies at the clinical level, but he was always eager to encourage basic research and was most proud of the work of Dr. Gamble. James Gamble was established in the Children's Hospital in Boston when he arrived. There was great mutual respect between these men and Blackfan took care to relieve Gamble from routine duties in patient care and teaching. His greatest personal involvement in research was in the field of hematology, which fascinated him.

Dr. Blackfan on ward rounds.

Certainly though, his greatest contribution must be considered his development of teachers and the stimulus for research of others in his department as it was finally organized.

In 1934, at the resignation of Dr. David Edsel, he was asked to consider whether he would accept the deanship of Harvard Medical School. The possibility of this position caused a great deal of painful thought and consideration on his part and he finally rejected it. He felt first that the deanship should be a full-time job and a full-time deanship was not proposed. What is more, he did not want to give up pediatries. I think he was finally influenced to remain as full-time chairman of the department of pediatries because of the definite feeling he got from some of us that we did not want him to accept the deanship. I remember well that I was asked how the staff would react to the move and, once he found that we did not want him to leave, he expressed immediately almost a feeling of relief, as well as great pleasure. Those of us consulted were proud of the honor offered to him but quite selfish in that we knew that he, as dean, would lean over backward in not favoring his own department, and also, of course, we begrudged the time it would take away from the hospital.

Dr. Blackfan's adult life was handicapped by a very severe illness. He had tic douloureux and had been operated upon by his friend, Walter E. Dandy. The operation left him with an anesthetic face, tongue, and eye, on one side. He rarely spoke of this to anybody, although at times the handicap was conspicuous and he was bothered by eye and sinus infections which could not easily be recognized. The final years of his life were complicated by neoplastic disease, which was extremely distressing to all his close associates, although he attempted to carry on his work with the same intense interest, if not physical capacity. He died from this condition November 29, 1941.

James L. Wilson

Comments on Current Literature

GROUP A BETA HEMOLYTIC STREPTOCOCCUS ASSOCIATED WITH NEPHRITIS

AN OUTBREAK of acute glomerulonephritis was observed on the Red Lake Indian Reservation in Northern Minnesota in the summer of 1953 which was shown to be associated with streptococcal infection, both scarlet fever and pyoderma.[1] There were sixty-three cases of acute glomerular nephritis, all occurring in children (age range, 15 months to 13 years), and concentrating in those of the late preschool and the early school years. More than one patient with nephritis in the family was not unusual, and in one instance four cases occurred within a single family.

An outstanding clinical feature of most of these cases of glomerulonephritis was the presence of a rather typical type of pyoderma which is described by the author in detail. "The lesions were characteristically distributed over the lower extremities and the lower half of the trunk. The individual lesion was round, slightly raised, pale red in color, and about five to seven millimeters in diameter. These lesions developed a small vesicle which was central in location with respect to the entire lesion, but which did not extend over the full area of the raised portion. The crust resulting from the rupture of the vesicle was flat and relatively thin. Seen at a later stage, when secondary infection had set in, the crusts were thicker, more irregular, and covered the entire area of the initial lesion."[1] These streptococcal infections responded well to penicillin, and a mass prophylaxis program carried out with penicillin was successful in eradicating the infectious agent from the general population of Red Lake. Only one fatality occurred among the sixty-three cases, a boy of 2 years who succumbed on the sixth day of illness. Renal involvement observed at autopsy was described as acute proliferative glomerulonephritis.

The unusual epidemiologic features of this outbreak of streptococcicosis, associated in a striking manner with acute glomerulonephritis and pyoderma, prompted a bacteriologic survey.[2] Personnel from the Communicable Disease Center, U. S. Public Service, Atlanta, Georgia, cooperating with the Minnesota State Department of Health laboratory, obtained skin and nasopharyngeal cultures from individuals at the Red Lake Indian Reservation, and from a "control" group composed of residents of the Cass Lake Indian Reservation, about fifty miles distant. Group A streptococci were isolated from forty-two persons of the Red Lake area, where the epidemic occurred, and from six individuals of the Cass Lake community where no overt epidemic of streptococcal disease had been reported. None of the forty-eight strains of group A hemolytic streptococcus obtained, forty-two from the Red Lake residents and six from the Cass Lake "control" group, could be typed by means of precipitating antiserums, 40 antiserums being available for use in the testing.

In order to establish, if possible, the antigenic characteristics of these forty-eight newly isolated, nontypable streptococci, antiserums to two strains were prepared by rabbit inoculation. One strain, designated as DS-C300,

had been isolated from the nose and throat of a child who was shown to have albuminuria, but who had not had clinical nephritis; the other strain, designated DS-C274, was obtained in almost pure culture from a skin lesion of another child who did have glomerulonephritis. The newly prepared C300 antiserum reacted with the majority of the forty-two Red Lake cultures, including the C274, and with three of the six cultures obtained in the Cass Lake area. "Of particular interest is the fact that the C300 antiserum reacted with twelve (92 per cent) of the thirteen cultures from children with clinical nephritis and with 17 (100 per cent) of the cultures from those with pyoderma, the two lesions most characteristic of the epidemic."[2] Preliminary tests using C274 antiserum gave similar results. On the basis of these experimental findings, the authors believe that "the C300 culture is representative of a serologically specific strain of group-A beta hemolytic streptococci, and that its antiserum has characterized the etiological agent of the Red Lake epidemic."[2] Unless further investigation should establish its identity with some type already recognized, the C300 strain seems to be a new type.

The association of this strain of group A beta hemolytic streptococcus with an epidemic outbreak of acute glomerulonephritis merits the attention of bacteriologists and clinicians, and suggests that this strain, together with types 12 and 4, must be included in studies concerning the relationship between group A streptococci and acute glomerulonephritis.

RUSSELL J. BLATTNER

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News and Notes

A new organization, the **Children's Exocrine Research Foundation,** has been formed to further research in cystic fibrosis of the pancreas. The Foundation announces that there will be no public drives for funds, but that it expects to obtain its funds from grants from other foundations and interested givers. The funds thus obtained will be allocated to research workers interested in the diseases of the exocrine system. The Scientific Advisory Board is composed of Sidney Farber, chairman, Rustin McIntosh, and Joseph Stokes. Dr. Paul Patterson is chairman of the publicity committee.

Applications for grants may be made to the headquarters of the Fund, 2300 Westmoreland St., Philadelphia, Pa.

In a small booklet announcing its formation is stated that the Foundation is entirely expense-free, and that no Foundation money is spent on materials, advertising, or salaries, and 100 per cent of the money raised is used to support research in this incurable children's disease.

The **National Association for Nursery Education** will hold its Bienniel Conference at the Hotel Statler, Boston, Mass., Oct. 19 through 22, 1955.

The Department of Pediatrics of **New York University College of Medicine** is offering a course in *tuberculosis* for pediatricians and general practitioners. This will be given by the Chest Clinic of the Children's Medical Service of Bellevue Hospital, five days, full time, Sept. 26 through 30, 1955. This course is designed for pediatricians or general practitioners interested in tuberculosis in infants and children. It will comprise lectures, clinical demonstrations and discussions of the diagnosis, prognosis and treatment of tuberculosis and other pulmonary disorders. Those interested should apply to Dr. Edith M. Lincoln, Bellevue Hospital, New York 16, N. Y.

Book Reviews

The Convalescent Child. Frank Falkner, M.R.C.S., Liverpool, 1952, The University Press, 55 pages.

A monograph from the Department of Child Health of the University of Liverpool based on a study of the convalescent care provided by a group of twenty institutions, chiefly in Great Britain. The author discusses the important place of home convalescent care and the special place of institutional care. The study goes into minute details of institutional care which are presented in a well-constructed chart. Based on his study, the author presents definite recommendations as to the control, architecture, and the care to be provided in convalescent homes. Although the importance of convalescent care is well recognized, it is a field that lies far behind the development of hospitals for children. The text has an excellent bibliography, and the monograph will be of great value to organizations and groups interested in this phase of medical care for children.

Ectopic Ureterocele in Infants and Children. Nils Olof Eriesson, Stockholm, 1954, Acta Chirurgica Scandinavia, 9 pages.

An excellent and beautifully illustrated monograph on ectopic ureterocele, based o

a study of twenty cases of ureterocele in children and twenty-nine in adults. Eriesson considers the condition as more frequent than usually supposed. The embryology, diagnosis, and treatment are discussed. Prognosis depends on the amount of renal damage that has occurred. If the diagnosis is made in infancy and the ureterocele resected, the prognosis is considered as rather good.

Moto-Kinesthetic Speech Training. Edna Hill Young and Sara S. Hawk, Stanford, Calif., 1955, Stanford University Press, 176 pages. Price $5.00.

The text describes the principles and application of the moto-kinesthetic method of speech correction developed by Mrs. Young. It has proved itself of use either as an adjunct to other methods, or as a method in itself. It consists of the vocalization of sounds required in speech through stimulation of the muscles involved in speech. This is an enlarged and rewritten text of an earlier volume published in 1938. Since that time many speech therapists have been trained in the "Hill-Young" school. It is of particular value to physicians interested in the speech correction of the handicapped child.

Die moderne Behandlung der Poliomyelitis im akuten Stadium. Herausgegeben von Prof. Dr. G. Fanconi, Basel, 1954, Benno Schwabe & Co., 70 pages. Price 8 fr. (Swiss).

A collection of seven papers, reprinted in brochure form, which were published in 1954 in the *Helvetica Paediatrica Acta*. Four of the seven contributions are from the Zurich group. Neukirch, in an extensive article, discusses in detail the treatment used at Copenhagen, and Engström the experience at the Infectious Disease Hospital in Stockholm. Thus the viewpoint of European specialists in the treatment of life-threatening polio is presented which makes the brochure of considerable interest. The problem discussed chiefly concerns the treatment of cases of polio presenting respiratory weakness and paralysis. Two of the articles from the Zurich clinic discuss the problem of artificial respiration with severe tetanus.

Feeding Your Child. Samuel M. Wishik, M.D., New York, 1955, Doubleday & Company, 223 pages. Price $3.50.

Another in the long and seemingly unending list of books written for parents on infant and child feeding. The reviewer can find nothing in it to set it apart from many of the other books on the subject. The author's style is rather discursive.

Das transversale Schichtverfahren. Doz. Dr. Med. Alfred Gebauer and Dr. Med. Alfred Schanen, Stuttgart, 1955, Georg Thieme, 343 pages. Price 97.50 DM.

The development of the laminograph, as it is usually referred to in the United States, has added a new technique in roentgenology. After a discussion of its development and the technical methods used, the authors discuss its application and use in the diagnosis and localization of various lesions, such as pulmonary tuberculosis, thoracic tumors, abdominal conditions, and skeletal changes. The text will be of chief interest to the skilled roentgenologist working in large clinics where the necessary apparatus is available. Incidentally, it is one of the best illustrated medical texts that has ever been published, and the publishers have added as much as the authors to its value.

Reactions With Drug Therapy. Harry L. Alexander, Philadelphia, 1955, W. B. Saunders Co., 301 pages. Price $7.50.

Coincident with the plethora of modern type drugs introduced in recent years, medical literature has been filled with reports of occasional toxic reactions following their use in therapeutic dosage. In this useful reference text, Alexander has systematized, according to their use or purpose, the reactions of "hypersensitivity" which have been noted following the use of specific drugs. Following introductory chapters on "Mechanisms," "Dermatologic Manifestations," and "Systemic Patterns" (of reaction), there are chapters on the chemotherapeutic and antibiotic anti-infectious drugs, sedative drugs, the antihistamines, serums and vaccines, plant products, and so on. The text is clear and well written, and each chapter is followed by a well-selected bibliography. It is a very useful compilation for the practitioner and fills a definite need.

HENRY GEORGE PONCHER
1902-1955

DR. Henry G. Poncher, a member of the Editorial Board of THE JOURNAL OF PEDIATRICS, died May 31, 1955, of heart disease.

Dr. Poncher was born February 15, 1902, at Odell, Illinois. After two years at Valparaiso University he entered on the study of medicine at the University of Michigan, receiving his M.D. degree in 1927. He interned, 1927-1928, at the Research and Educational Hospital of the University of Illinois in Chicago and the following year was resident in pediatrics. In 1928 he was appointed instructor in pediatrics in the Medical School, and progressed through associate and assistant professorships until appointed professor in 1941. In 1945 he became head of the department. In 1953 he resigned to enter private practice at Valparaiso, Indiana, and became professor of human biology and director of student health at Valparaiso University.

Among the national medical societies in which he held membership were the following: American Pediatric Society, American Academy of Pediatrics, Society for Pediatric Research, Society for Research in Child Development, Society of the Sigma X, and the Alpha Omega Alpha honorary medical fraternity. At the time of his death he was a member of the Council of the American Pediatric Society, and one of the nine members on the American Board of Pediatrics.

His chief pediatric interests were in the fields of therapeutics and hematology and he made many contributions to pediatric literature based on his research and clinical observations. For several years he edited the *Yearbook of Pediatrics*. He had been an active member of the Editorial Board of the JOURNAL since 1948.

In 1928 he married Gretchen C. Marquart. He is survived by his widow and one son, John Robert Poncher.

Editor's Column

THE TREATMENT OF ECZEMA

IT IS with great pleasure that the JOURNAL, in this issue, publishes the first installment of a five-part discussion of the "Treatment of Eczema" by Dr. Lewis Webb Hill. Dr. Hill for many years was head of the Allergy Clinic of the Children's Medical Center in Boston, and has an unparalleled experience in the treatment of eczema in infants and children. He is recognized as an authority on the subject by pediatricians, allergists, and dermatologists. This series of papers sums up the conclusions he has reached, based on a vast experience over many years. His discussion is "personal" and informal, but he has avoided the pitfalls of indecisiveness and wandering off the track which so often are found in an informal discussion. It is planned to publish the articles in book form, and, hence, reprints will not be available from Dr. Hill or the JOURNAL.

THE HAZARDS OF BLOOD TRANSFUSION

THE wide usefulness of blood transfusion has been well established. That the procedure is not without danger has been emphasized in recent papers.[1-4]

Vogel[1] points out that the risk of transmitting syphilis, always a small one, is much less at present as the prevalence of syphilis has fallen. Moreover, the *Treponema pallidum* is destroyed in refrigerated blood after four days.

Malaria is a much greater hazard. Plasmodia, particularly quartan, may persist in the blood for years after the initial episode. The parasite is not destroyed by storage or by refrigeration.

Massive contamination of blood is a serious problem. From 2 to 5 per cent of blood bank donations are contaminated with bacteria. Most bacteria do not grow readily at icebox temperature, but the products of bacterial degradation may lead to a marked pyrogen reaction. Some bacteria, notably the gram-negative chromogens, grow readily at 4° C. and have produced fatal transfusion reactions.

Far and away the most serious problem in blood bank transfusions is the danger of transmitting homologous serum jaundice. Careful screening of donors, efforts at destroying the virus by drugs and by ultraviolet irradiation, tests for virus in the stored blood, have proved inadequate to eliminate this hazard.

Though potent serums are now available for cell grouping, errors are still made, and cell grouping for both donor and recipient should be confirmed by means of a serum typing. A weakly reacting Rh-positive blood,

which gives negative results by the usual methods, may immunize an Rh-negative woman so that she will be prevented from bearing normal children. Also blood from such a donor may give a fatal hemolytic transfusion reaction in an Rh-negative woman who is already immunized to Rh antibodies. Vogel urges that the most reliable method—the indirect antiglobulin test—be used since the ordinary method of saline matching is unreliable in detecting many of the new blood factors which may produce serious transfusion reactions.

Though Rh-negative, type O blood is the safest to use in emergencies, it is not without danger. Such blood may produce a hemolytic reaction through destruction of the recipient's cell by anti-A and anti-B in the donor's plasma. This danger can be eliminated by withdrawing the plasma immediately before transfusion.

A febrile reaction is one of the commonest but, fortunately, one of the least serious reactions following transfusions. Fever may occur during the transfusion or shortly thereafter. The reaction is usually mild but there may be a chill with a rise of temperature up to 105° F. The fever ordinarily returns to normal after several hours. Post-transfusion febrile reactions have been greatly reduced by using reliable, disposable collection and administration equipment.

Circulatory overload is an occasional complication of transfusion. It can be serious. The symptoms, which may occur during or shortly after transfusion are dyspnea, orthopnea, cyanosis, cough, and moist râles in the chest.

Allergic reactions follow transfusions in about 1 to 5 per cent of cases. The reactions are generally mild and consist of urticaria, occasionally angioneurotic edemia, rarely asthma. Vogel recommends the addition of pyribenzamine or Chlor-Trimeton to the blood before administration as a prophylactic. Antihistamines, used in this way, also depress the chills and fever which many patients experience after transfusion.

Davidsohn[2] estimates that, even in the best-run institutions, the mortality rate from transfusions is approximately one in from 1,000 to 3,000 transfusions. Since roughly 3,500,000 transfusions are given each year, the number of transfusion deaths is about 1,700 a year, or about as many as die from appendicitis.

According to Robertson[3] the number of transfusions given to children in a large New York City voluntary teaching hospital has fallen steadily from 1,462 in 1950 to 1,006 in 1953. He attributes this principally to a wider appreciation of the hazards of transfusion and to the greater availability of substitutes for, and derivatives of, whole blood. Moreover, the steroid hormones and antileukemic drugs have lessened the need for whole blood in the treatment of the leukemias and purpuras.

H. B.

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